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NONSUPPURATIVE POSTSTREPTOCOCCIC (RHEUMATIC) PNEUMONITIS

Pathologic Anatomy and Clinical Differentiation from Primary Atypical Pneumonia

COMMANDER CLYDE R. JENSEN (MC), U.S.N.R.

CLINICAL recognition of pulmonary lesions in rheumatic fever is increasing. Many careful descriptions of the pathologic anatomy of rheumatic pneumonitis, obtained from cases in which death was due to rheumatic carditis, have finally brought into focus what seems to be a highly characteristic picture, gross and microscopic, now generally familiar to pathologists. Pathologic details may not be so familiar to most clinicians. It is not yet possible, however, to identify the disease solely on the basis of a single anatomic change in the lungs alone—to recognize any one feature as pathognomonic. This is due somewhat to the fact that rheumatic fever is always a disease of many organs, and when only a part of the picture is viewed either clinically or anatomically in one organ at a time it seems to blend with other conditions, usually regarded as separate diseases.

So far as this concerns the pulmonary lesion, the pathologic picture found in rheumatic fever may easily be confused with that of other conditions, in particular with that found in primary virus infections of the respiratory tract. Clinical confusion also is likely. In order to explain this fact better, an unusual case is here selected for presentation in which death in the acute stage of rheumatic fever resulted primarily from the pulmonary lesions of this disease, unaccompanied with significant cardiac involvement. The pathologic changes in the lungs and kidneys will be given in detail, to be used as the basis for illustrating the general tissue lesions of rheumatic fever and for discussing the task of differentiating clinically between rheumatic penumonitis and conditions which it may simulate.

Read at the meeting of North Pacific Society of Internal Medicine, Seattle, April 28, 1945.

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REPORT OF A CASE

Clinical History.—The patient was a 19 year old seaman. His past health had always been good except for numerous attacks of tonsillitis in childhood, with nothing to suggest rheumatic fever. The present illness began aboard ship on Dec. 21, 1944, with a typical attack of scarlet fever, observed by a medical officer. He seemed to recover promptly and returned to full duty in ten days. On Jan. 5, 1945, fifteen days after the onset of the pharyngitis of the scarlet fever, while otherwise well, he began to have pain in one hip. On January 10 severe pain and swelling appeared in both ankles also, along with tenderness in the muscles of the neck and slight shortness of breath. On January 12 he was transferred to a Naval hospital. At this time, aside from the slight shortness of breath and acute pain and swelling in the ankles, there were slight puffiness of the hands and face, numerous erythrocytes and casts in the urine and moderate albuminuria. With rest and heavy doses of sodium salicylate the symptoms referable to the joints receded in four days, but the slight generalized edema and shortness of breath continued. The blood pressure was 165 systolic and 105 diastolic. With an intake of fluid maintained between 2,000 and 3,000 cc. daily, the output of urine remained always over 1,000 cc. daily. The blood nonprotein nitrogen was 60 mg. per hundred cubic centimeters on admission, falling to 25 mg. just before death. Shortness of breath continued unchanged until January 18, when severe dyspnea and cyanosis began, and he had to be kept continually under oxygen during the remaining two days of life. Rales were audible throughout the lungs. Repeated physical examinations failed to show evidence of cardiac enlargement or murmurs, and the final electrocardiogram, three days before death, was normal. He died in great respiratory distress on Jan. 20, 1945, exactly thirty days after the onset of the acute pharyngitis and fifteen days after the first appearance of rheumatic pain.

Observations at Autopsy.—Gross: All organs were grossly as in health except the lungs, kidneys and spleen. The spleen was large, weighing 340 Gm., and was uniformly soft and purple. The kidneys were darker red than normal and contained many minute purple spots in the subcapsular surface; otherwise they were normal.

Lungs. Each pleural cavity was free of adhesions and contained only a small amount of thin fluid. The pleural surfaces were glistening except for a few small dull patches. Large bronchi contained much moderately thick dark red fluid; their mucosa was dark gray-red. The main divisions of the pulmonary artery were free of clots. The lungs together weighed 1,990 Gm. and were essentially alike. Peribronchial lymph nodes were large, soft and gray-black. The lung parenchyma throughout varied from red to dark plum-purple and was only slightly crepitant. The darker purple regions were not clearly demarcated and were irregularly distributed, and such regions particularly were rather solid but not hard, more resilient than friable. Only a small amount of thin, bloody fluid ran freely from the cut surface, but much could be expressed with pressure.

Microscopic: Lungs (fig. 1). In all sections the picture was essentially the same. Few alveoli contained air. Many of them were filled with homogeneous material characteristic of edema fluid, and most of them contained cells also. Many of the cells were large mononuclear cells of phagocytic type, some containing a few fine spots of brown pigment, but so-called heart failure cells, heavily

laden with brown pigment, were sparse. In some alveoli were desquamated chains of septal cells, mixed in places with amorphous debris. In many places there was a thick, eosinophilic hyaline membrane along the periphery of alveolar ducts, seemingly fixed as a lining to the wall, often partially surrounding an air pocket. In many places there were numerous erythrocytes free in the alveoli, indicating recent capillary hemorrhage, but in no place was this hemorrhage dense over a large area. Mononuclear cells predominated in the exudate. Mingled with them were varying numbers of polymorphonuclear leukocytes, usually sparse, nowhere

Fig. 1.—Lung. Engorgement of capillaries, exudation of mononuclear cells, edema and hyaline membrane partially lining two alveolar ducts. Low power (× 130).

heavy. Capillaries were engorged. Alveolar walls contained many mononuclear cells, some recognizable as lymphocytes and many as swollen endothelial or other large mononuclear cells. In some places there were small but dense collections of lymphocytes and plasma cells. There were strands of fibrinous material extending from some alveolar walls into the spaces. Interstitial edema was particularly noticeable in larger septums, and here also there were many focal infiltrations

of lymphocytes and plasma cells, sometimes with a few histiocytes and leukocytes. Although rarely a giant cell with hyperchromatic and irregular nucleus was encountered, nothing resembling a true Aschoff nodule was found. No organisms were identified with the MacCallum-Goodpasture stain.

Kidneys (fig. 2). About 15 per cent of the tubules were filled with blood. Others contained finely granular debris, and a few contained hyaline casts. There was little edema in the interstitial tissue generally, but there were many small regions of capillary hemorrhage, some with demonstrable rupture directly into a tubule (fig. 3). In such regions, disintegration of tubular epithelium was recog-

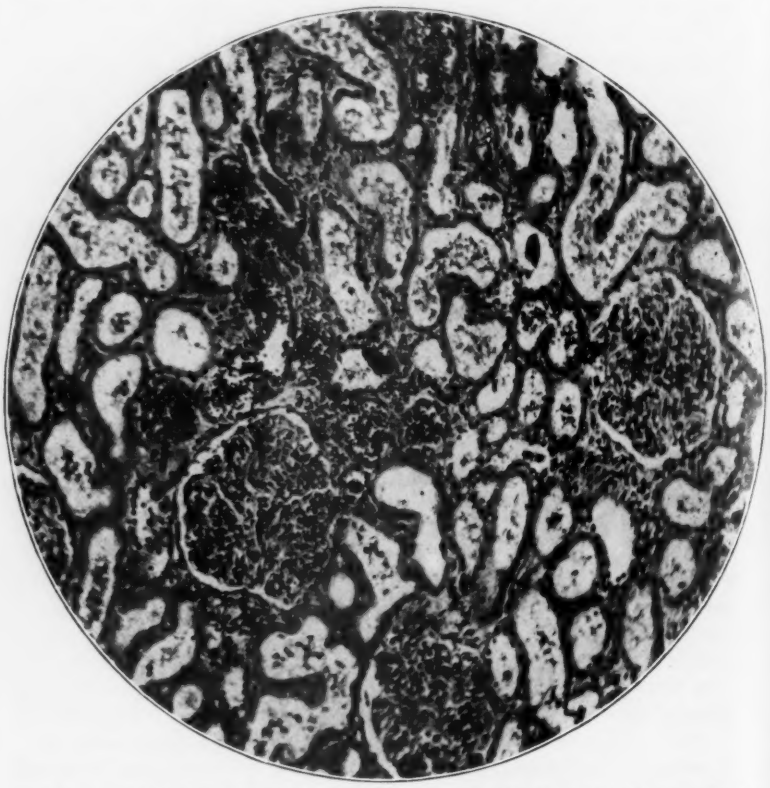

Fig. 2.—Kidney. Glomeruli relatively normal; blood cell casts in several tubules. Low power (× 130).

nizable, but tubular epithelium otherwise was normal throughout. There were other small regions in which there were focal collections of lymphocytes and plasma cells in the interstitial tissue (fig. 4). There was no hemorrhage in such regions, suggesting that they were older lesions than those of hemorrhage and might not have been preceded by actual hemorrhage. Some of these collections of cells were around small veins, and a few were subintimal in medium-sized veins, producing a bulge in the intima. Most of the glomeruli were rather bloodless, their capil-

lary channels collapsed and the nuclei still vesicular and perhaps slightly swollen but without proliferation. Rarely there were a few erythrocytes free in a glomerular space, in contrast to the relative profusion of blood in the tubules.

Heart. Under the pericardium and endocardium there were small collections of lymphocytes and plasma cells, about equal in numbers and in the pericardial fat these had a perivascular arrangement (fig. 5). There were rare plasma cells and lymphocytes in perivascular fibrous tissue in the myocardium but no dense cell collections here.

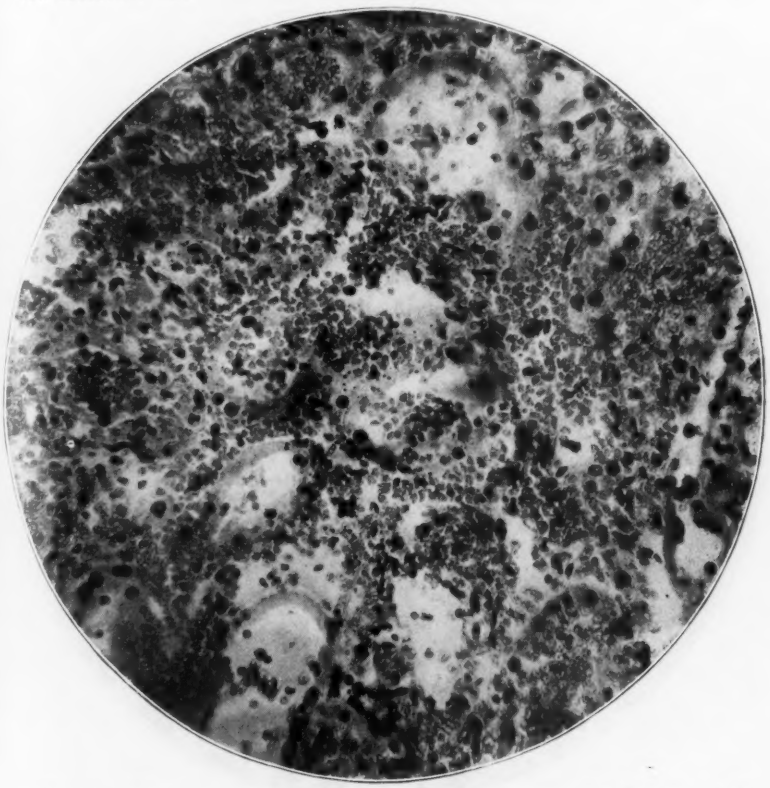

Fig. 3.—Kidney. Capillary hemorrhage with direct rupture into tubules. High power (× 380).

Other organs. In sections from the liver (fig. 6), pancreas, testicles, synovial tissue of the left ankle, suprarenal glands and spleen, there were small scattered collections of lymphocytes, sometimes with plasma cells, similar to those in the pericardium, but nowhere were the changes so prominent as in the lungs and kidneys. Of several sections from the brain, one from the hypothalamic region contained two small perivascular hemorrhages but no cell infiltrations.

Comment.—Cultures of the original throat infection were not made, but the fact that the patient had typical scarlet fever is enough evidence

that he was infected with a hemolytic streptococcus. He died in the postinvasive, nonsuppurative stage of this infection, having had concurrently three prominent sequels of such infection, acute hemorrhagic nephritis, acute arthritis and acute pneumonitis. At the time of death the articular symptoms had subsided. It is not unusual for such symptoms to subside sooner than those referable to other organs, possibly because joints are so easily put at complete rest.

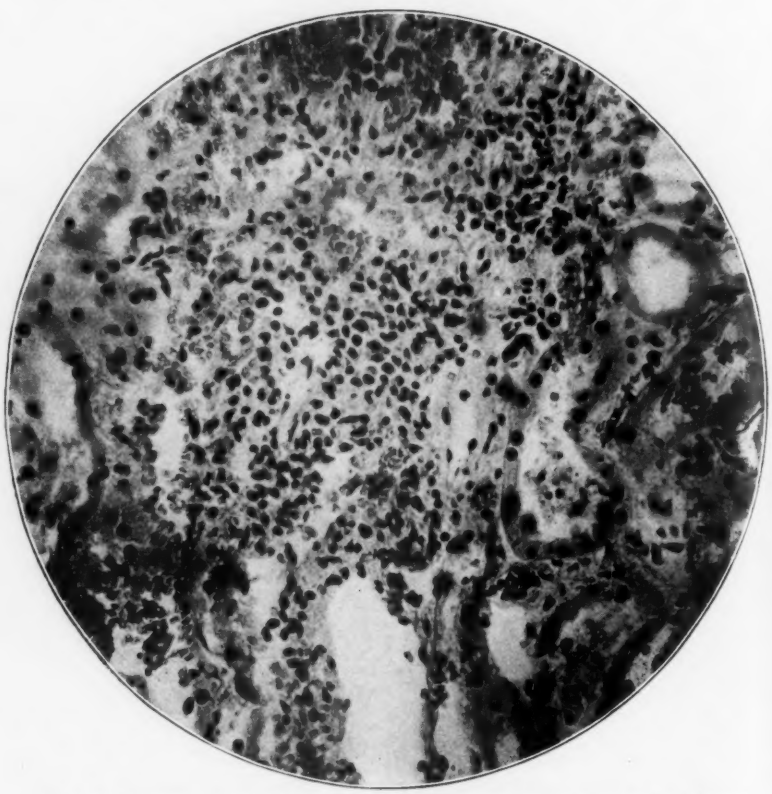

Fig. 4.—Kidney. Focal infiltration of lymphocytes and plasma cells between tubules.

Death from any cause is unusual in the early stages of rheumatic fever, but when it does occur rheumatic carditis with heart failure is the usual mechanism. In the present case, there was no clinical evidence of cardiac involvement. At the autopsy there was no gross pericarditis or endocarditis, and the heart was not enlarged. Microscopically the cellular infiltrations in the pericardium and endocardium

were small and scattered and not more impressive than those in other organs, such as the liver, where they could not reasonably be regarded as evidence of enough disease to affect seriously the function of the organ.

The problem arises of weighing the relative importance of the renal and the pulmonary lesions in causing death. The sustained urinary output and the receding azotemia indicate clearly that the patient did not die in a state of renal insufficiency. The slight generalized edema

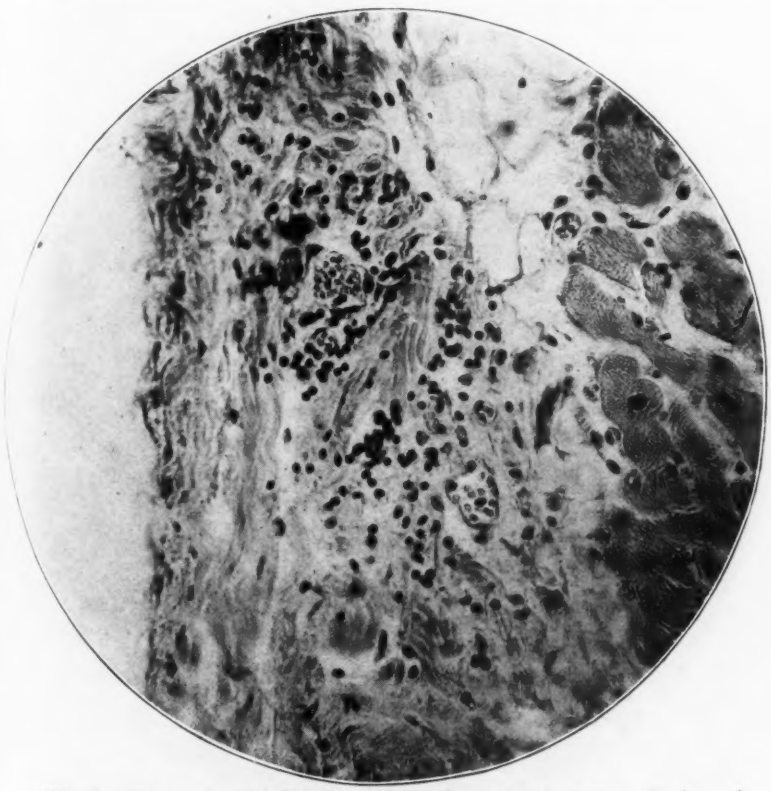

Fig. 5.—Heart. Small infiltrations of lymphocytes and plasma cells in pericardium. High power (× 380).

with lowered serum protein indicates edema chiefly from deficiency of albumin in the circulating blood. Some of this albumin was lost through the kidney. Much of it may well have been into the pulmonary space, as careful attention to the weight and the microscopic pathologic changes of the lungs will show. It seems impossible to assign the kidneys more than a secondary role in causing death. The clinical impression of death due primarily to pneumonitis was fully sustained by the

observations at autopsy. Such a case afforded an unusual opportunity to study the pulmonary lesions of rheumatic fever uncomplicated by secondary infection or by the changes secondary to heart disease.

NONSUPPURATIVE TISSUE LESIONS FOLLOWING STREPTOCOCCIC INFECTIONS

When pulmonary lesions occur in rheumatic fever, they are fundamentally like those occurring elsewhere in the body at the same time.

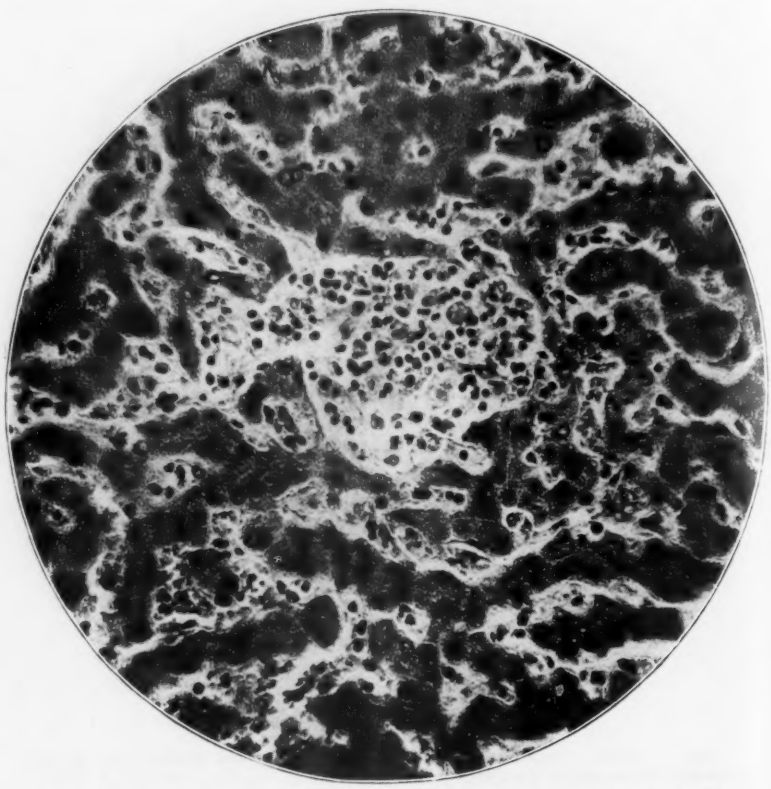

Fig. 6.—Liver. Small focal collection of lymphocytes and plasma cells, illustrative of the small lesions in many organs. High power (× 380).

The general similarity of the lesions in acute hemorrhagic nephritis, acute rheumatic carditis, chorea and many other conditions known to follow hemolytic streptococcus infections, has long been recognized. Some review of these general pathologic changes may be desirable to clarify the discussion of rheumatic pneumonitis which will follow

Of all persons who contract an infection with a hemolytic streptococcus, the great majority recover promptly and completely. Most such infections occur in the upper respiratory tract. The initial stage of acute invasion is a stage of suppuration, at least microscopically, and a small percentage of patients have additionally an immediate suppurative complication, such as lymphadenitis or otitis media. Particularly when the portal of entry is elsewhere than the upper respiratory tract, as in puerperal infection, a few may die after an acute, fulminating course, a septicemia. In such cases, streptococci are easily recoverable from the blood during life and demonstrable after death in the tissues, within capillaries or beyond the endothelial barrier, undergoing active phagocytosis by leukocytes or by cells of the reticuloendothelial system.

In a few who apparently recover or are recovering well from the acute invasive and suppurative stage there develop after a short clinical delay symptoms of nonsuppurative disease somewhere in the body. This latent period or delay varies from a few days to a few weeks. It is usually an afebrile period, but, particularly when the suppurative stage has been prolonged, it may not be perceptible clinically as a period of improvement. Depending on the organ or tissue most involved, this nonsuppurative stage may be expressed as acute arthritis, acute rheumatic carditis, acute hemorrhagic nephritis, acute encephalitis (chorea) or acute pneumonitis, frequently with manifestations less well defined or at least less well named as specific diseases, such as purpura, urticaria, erythema and generalized mild edema without much nephritis. Combinations are frequently present in a given subject.

Death in the latent period or in the early stages of the nonsuppurative sequels is so unusual that autopsies allowing study of the lesions are scarce. Study of them has been further hampered by the fact that the diseases concerned, such as acute rheumatic fever and acute hemorrhagic nephritis, were long regarded as unrelated processes. Realization has been slow in arriving that they are probably always relatable to an antecedent streptococcic infection, perhaps so mild as to escape attention as such.

Brody and Smith [1] and Mallory and Keefer [2] have reviewed the subject of these lesions and have added valuable contributions of their own from fatal cases of hemolytic streptococcus infections of various clinical types, scarlet fever, erysipelas, puerperal sepsis and cellulitis. Beginning a few days after the onset of the infection, there appear in many tissues foci of cellular infiltration composed chiefly of lymphocytes and plasma cells, with a few leukocytes often present and occasion-

1. Brody, H., and Smith, L. W.: The Visceral Pathology in Scarlet Fever and Related Streptococcus Infections, Am. J. Path. **12**:373-394 (May) 1936.

2. Mallory, G. K., and Keefer, C. S.: Tissue Reactions in Fatal Cases of Streptococcus Haemolyticus Infection, Arch. Path. **32**:334-355 (Sept.) 1941.

ally a few eosinophils. The lesions are basically the same in all organs, regardless of whether the initial infection is in the form of scarlet fever or of another clinical type.

These lesions do not contain organisms and do not become abscesses. Preceding the actual infiltration of cells, there is localized damage of tissue. "Collagen necrosis" is a more specific term, preferred by the pathologist. If this is in a highly vascular organ or involves the wall of a small vessel, petechial hemorrhage is likely. Thus the petechial hemorrhage is the earliest lesion easily recognizable, although the peculiar focal collections of cell types previously described are more characteristic. Early and late lesions may be found in the same organ, indicating repetition in different places. The Aschoff nodule is a slightly later lesion, a special form of it occurring in the heart. It probably does not acquire its complete characteristics, detailed descriptions of which are so cherished by the histopathologist, until at least three weeks after the clinical onset of rheumatism.

The lesions are perhaps more plentiful in the heart and kidneys in most cases, although naturally these organs have received more attention because of the rather distinct clinical syndromes produced when either one or the other is predominantly involved, acute rheumatic carditis or acute hemorrhagic nephritis. Many of the lesions are in close relation to the vascular system, near small arteries, sometimes subintimal in veins and subendocardial in the heart. This relation to the vascular system is one reason that kinship is believed by some to exist between rheumatic fever and conditions such as periarteritis nodosa and generalized lupus erythematosus. The impossibility of resting the heart muscle or its valves completely may in part determine the usual frequency of lesions in it, and the great vascularity and unceasing activity of the kidneys may condition the frequency and prominence of lesions in these organs. But anatomy alone does not explain the observed variations in involvement of organs. Neither does there seem to be any connection between the organ involved and the particular strain of hemolytic streptococcus causing the initial infection, although this phase of the problem has not yet received exhaustive study.

Although connection between these nonsuppurative lesions and hemolytic streptococcus infection may be regarded as established, many phases of this relationship are still mysterious. Their general similarity to certain lesions occurring in anaphylactic states has long been noted. In recent years, Rich and Gregory [3] have stressed the factor of anaphylaxis in rheumatic fever and have secured admirable reproductions in rabbits

3. Rich, A. R., and Gregory, J. E.: On the Anaphylactic Nature of Rheumatic Pneumonitis, Bull. Johns Hopkins Hosp. **73**:465-478 (Dec.) 1943; Further Experimental Cardiac Lesions of the Rheumatic Type Produced by Anaphylactic Hypersensitivity, ibid. **75**:115-134 (Aug.) 1944.

of the cardiac lesions by sensitization with foreign protein. Todd [4] and Coburn and Pauli [5] have studied the abnormal rise in serum antibodies coincident with the appearance of symptoms in rheumatic fever. Investigations in this field demonstrate that the lesions in this disease must be related in some way to abnormal antigen-antibody reactions, and thus rheumatic fever at last seems firmly bound to the hemolytic streptococcus. Opportunity may still remain to uncover some additional infectious agent, perhaps working in harmony with the streptococcus; but it is difficult to understand how the bond between rheumatic fever and the streptococcus can ever be entirely broken. No attempt will be made here to discuss at length this aspect of the problem because it is aside from the primary purpose of this paper.

PULMONARY LESIONS IN RHEUMATIC FEVER

It is probable that the pulmonary lesions are seldom extensive. It is possible that their importance is sometimes overlooked, particularly when they occur without other manifestations of rheumatic fever to call attention to their true nature. With this possibility as justification, detailed discussion of rheumatic lesions as they occur in the lung will now be given.

The lesions in the lung are not fundamentally different from those occurring elsewhere: focal damage of tissue, edema, possible capillary rupture, cellular infiltrations and efforts at healing. The immediate consequences of this in the lungs may be remarkably different from those in other organs, particularly if the lesions are severe. As naked exposure as possible of the capillaries to the air is the primary mission of the lung. Stroma is reduced to the necessary minimum around the alveolar capillary. This offers unusual opportunities for exudative phenomena. Partial damage to a capillary wall leads to the escape of small amounts of fluid higher in protein than simple edema fluid. With severer damage, there is capillary rupture and hemorrhage. In either case the release of fluid is easier than with a comparable degree of damage in a more solid organ. Further, such escaped fluid is dispersed easily in the porous lung, assisted by respiratory movements of lung and air, sometimes to points remote from the place of release. This accounts for the frequent finding of blood or the hyaline membrane in microscopic fields where there is no apparent capillary damage or

4. Todd, E. W.: Antihaemolysin Titres in Haemolytic Streptococcal Infections and Their Significance in Rheumatic Fever, Brit. J. Exper. Path. **13**:248-259 (June) 1932.

5. Coburn, A. F., and Pauli, R. H.: Studies on Relationship of Streptococcus Hemolyticus to Rheumatic Process: Observations on Immunological Responses of Rheumatic Subjects to Hemolytic Streptococcus, J. Exper. Med. **56**:651-676 (Nov.) 1932.

cellular infiltration, for the hyaline membrane is merely partially inspissated fluid of higher protein content than usual edema fluid, impacted against the lining of the air ducts by forcible inspirations. The kidney is also a highly vascular organ, and in one way the manifestations of this disease in it are roughly comparable to the situation in the lung. Many renal capillaries are so close to an open tubular system that capillary seepage, whether as albuminous fluid or as whole blood, is unimpeded once the tubular wall is penetrated or broken. For purposes of exposition only, the hyaline membrane of the lung may be likened to the hyaline cast of the kidney tubule. Coburn [6] has shown that with routine Addis counts of the urinary sediment one may detect abnormal hematuria in most cases of rheumatic fever, indicating that in most cases there is renal involvement. A comparably sensitive test of the lungs might give surprising results. Exudative changes would have to be considerable to show roentgenographically.

SIMILARITY BETWEEN PATHOLOGIC CHANGES OF RHEUMATIC PNEUMONITIS AND OF VIRUS PNEUMONITIS

While pneumonitis is being more frequently recognized in cases of severe rheumatic fever, it is not often described as dominating the clinical picture. Since rheumatic carditis is sometimes recognized as occurring without arthritis and since acute nephritis frequently occurs in the postinvasive stage of streptococcic infection, with or without arthritis, there is no good reason why pneumonitis should not occur sometimes as the only prominent clinical exhibition.

It is my belief that this occurs more often than is suspected and that the condition is mistaken for virus infection of the lungs. An illustrative case is that of a young man known to have had a normal heart at the time of his enlistment in the Navy and later at the time of his admission to a Naval hospital with a diagnosis of primary atypical pneumonia. No rheumatic pains were noted at the time. He was discharged as well and fit for duty after twenty-six days, after a clinical course that might be described as average for this condition. Nine months later he was readmitted to the hospital with well advanced mitral and aortic valvular lesions. Review of the older record then indicated that the only reasonable explanation of the former pneumonitis was that it was the only prominent clinical manifestation of "rheumatic" fever which he had at the time. When one examines the literature on primary atypical pneumonia, with particular attention to protocols of cases, suggestive evidence is sometimes encountered that some of the cases included under this term may well have been cases of rheumatic pneu-

6. Coburn, A. F.: Relationship of the Rheumatic Process to the Development of Alterations in Tissues, Am. J. Dis. Child. **45**:933-972 (May) 1933.

monitis unrecognized as such. Thus one author,[7] reviewing 32 cases, described 1 in which a cold in the head preceded the onset of pneumonitis by ten days and the heart was without murmurs at the onset of the illness, but after a protracted convalescence of two months a presystolic murmur and cardiac enlargement led to the conclusion that the patient had had rheumatic heart disease. In another report[8] the authors, reviewing 52 cases of what would now be called primary atypical pneumonia, mentioned a group of 6 cases in which the primary disease was "complicated by a variety of phenomena suggesting that tissues other than the pulmonary alone were involved. Among these phenomena were migratory polyarthritis, erythematous skin eruptions, slight enlargement of the spleen and lymph glands, jaundice, gross hematuria, fibrinous pericarditis and encephalitis." In a fatal case from this series, periarterial lesions suggesting periarteritis nodosa were found. Examples such as these are cited merely as evidence for a suspicion that conditions of diverse origins have been unwittingly grouped together under the poor term "primary atypical pneumonia," and that at least a small proportion of such cases have been cases of rheumatic pneumonitis without much rheumatism. I freely admit a suspicion of my own guilt in this respect, and I wish that I now had available for reevaluation records of several cases in my own experience in recent years.

That the clinical resemblance between rheumatic pneumonitis in some cases and pneumonia due to virus infection may depend more than is realized on a rather striking resemblance of pathologic anatomy may be emphasized by a brief chronologic review of the development of our knowledge of them.

Pathologic Changes of Influenzal Pneumonia.—The pathologic changes of influenzal pneumonia in 1918-1919 were described by many authors and particularly well by MacCallum,[9] Goodpasture and Burnett[10] and Wolbach.[11] The essential lesion was that of damage to tissue with rupture of capillaries, formation of hyaline membrane and infiltrations of mononuclear cells. In severely ill patients dying quickly, hemorrhage was the prominent feature. In those surviving longer, secondary infection with pyogenic organisms was the rule, and there

7. Longcope, W. T.: Bronchopneumonia of Unknown Etiology (Variety X), Bull. Johns Hopkins Hosp. **67**:268-305 (Oct.) 1940.

8. Kneeland, Y., Jr., and Smetana, H. F.: Current Bronchopneumonia of Unusual Character and Undetermined Etiology, Bull. Johns Hopkins Hosp. **67**:229-267 (Oct.) 1940.

9. MacCallum, W. G.: Pathology of Pneumonia Following Influenza, J. A. M. A. **72**:720-723 (March 8) 1919.

10. Goodpasture, E. W., and Burnett, F. L.: The Pathology of Pneumonia Accompanying Influenza, U. S. Nav. M. Bull. **13**:177-197, 1919.

11. Wolbach, S. B.: The Pathology and Bacteriology of Fatal Influenza Cases at Camp Devens, Bull. Johns Hopkins Hosp. **30**:104-109 (April) 1919.

was corresponding leukocytic or suppurative exudation. Either excessive hemorrhage or much suppuration tended to blur the underlying picture. For a long time this picture, particularly when the hyaline membrane was present, was regarded as almost pathognomonic of influenzal pneumonia.[12] Farber and Wilson[13] in 1932 demonstrated the true mechanism of production of this membrane and so its lack of specificity. It is now realized that while this membrane is not usually observed by histologic examination in routine autopsies and should arrest attention when encountered, it is not pathognomonic of any one disease.

Rheumatic Pneumonitis.—The characteristic pathologic changes in rheumatic pneumonitis were first described with reasonable clarity by Naish,[14] in 1928, and by Gouley and Eiman,[15] in 1932. More recently, Epstein and Greenspan[16] have further elaborated the description of these changes and have traced the evolution of the lesions beyond the acute phase. In all descriptions there is much similarity to the basic lesions in influenzal pneumonia.

Primary Atypical Pneumonia.—Under this awkward term there have been described in recent years many cases of pneumonia not caused by an identified organism and often thought due to a virus, although there is no agreement that a specific virus has been isolated. There are several reports of the pathologic anatomy of this based on 1 or a few cases, but that of Golden,[17] based on 42 acceptable cases from the United States Army, is the most comprehensive. The lesions may be complex, depending on the duration and probably on the presence or absence of secondary infection. Generally the descriptions resemble those given of influenzal pneumonia in 1919, although there are few instances of the acute, fulminating form of the disease in which the patient dies quickly with wet, bloody lungs, so common in the epidemic of that time. Probably because in few of the fatal cases have the patients died quickly, suppurative bronchiolitis with bronchopneumonia is a prominent observation, but the focal tissue lesions with infiltrations of mononuclear cells are also present.

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12. Goodpasture, E. W.: The Significance of Certain Pulmonary Lesions in Relation to the Etiology of Influenza, Am. J. M. Sc. **158**:863-870 (Dec.) 1919.

13. Farber, S., and Wilson, J. L.: The Hyaline Membrane in the Lungs: II. An Experimntal Study, Arch. Path. **14**:450-460 (Oct.) 1932.

14. Naish, A. E.: The Rheumatic Lung, Lancet **2**:10-14 (July 7) 1928.

15. Gouley, B. A., and Eiman, J.: The Pathology of Rheumatic Pneumonia, Am. J. M. Sc. **183**:359-381 (March) 1932.

16. Epstein, E. Z., and Greenspan, E. B.: Rheumatic Pneumonia, Arch. Int. Med. **68**:1074-1094 (Dec.) 1941.

17. Golden, A.: Pathologic Anatomy of "Atypical Pneumonia, Etiology Undetermined": Acute Interstitial Pneumonitis, Arch. Path. **38**:187-202 (Oct.) 1944.

Other Virus Pneumonias.—The pathologic changes in certain rare types of virus pneumonia, so far as they have been well described, are in general like those in influenzal pneumonia. In psittacosis distinctive inclusion bodies are found, and in certain rare types of pneumonia in infants inclusion bodies have been described by experienced observers,[18] but in influenzal pneumonia and in the disease now called primary atypical pneumonia true inclusion bodies are not present. Thus most types of virus infections in the lung leave no individual signatures observable by histologic examination.

General Comment on Pathologic Changes.—Much time has here been devoted to pathologic anatomy because one must understand this well in order to understand any disease and because often one must use it as a point of departure, at least, in arranging any scheme for differential diagnosis. The manner of this presentation has been purposely arranged to emphasize similarities, to warn of the pitfalls that may await if one attempts to depend too much on physical findings or roentgenographic appearance or even the general clinical course in cases of mild infections in which similarities are particularly striking.

The emphasis here given to the resemblance between rheumatic and virus pneumonitis may seem to revive the question of virus origin of rheumatic fever. It is not so intended. Some may still be dissatisfied with the streptococcus as the sole culprit in rheumatic fever, and recent observations[19] have suggested the possibility of a virus agent. Discussion of this is purposely avoided here because the final answer is not obtainable from anatomic changes alone, which this presentation stresses. Admittedly not all aspects of the disease which is today called rheumatic fever are clear. The subject of primary atypical pneumonia also is confusing. But enough is known so that better attempts might be made to sort cases, if only in terms of current terminology.

CLINICAL DIFFERENTIATION BETWEEN RHEUMATIC PNEUMONITIS AND PRIMARY ATYPICAL PNEUMONIA

Since the anatomic pictures of primary atypical pneumonia and of that occurring as a nonsuppurative sequel to hemolytic streptococcus infection are so alike, it is little wonder that clinical distinction between them may be difficult if there is no clue outside the lungs. In each

18. Goodpasture, E. W.; Auerbach, S. H.; Swanson, H. S., and Cotter, E. F.: Virus Pneumonia of Infants Secondary to Epidemic Infections, Am. J. Dis. Child. **57**:997-1011 (May) 1939.

19. Eagles, G. H.; Evans, P. R.; Fisher, A. G. T., and Keith, J. D.: A Virus in the Aetiology of Rheumatic Diseases, Lancet **2**:421-429 (Aug. 21) 1937. Eagles, G. H., and Bradley, W. H.: Agglutination of Suspensions of Virus-Like Particles Prepared from Exudates in Acute Rheumatic Fever, Quart. J. Med. **8**:173-184 (April) 1939. MacNeal, W. J.; Blevins, A.; Slavkin, A. E., and Scanlon, H.: Experimental Verrucous Endocarditis, Science **101**:415-416 (April 20) 1945.

there is fever and cough, with hemoptysis if the condition is severe. Physical and roentgenologic signs are similar, with a tendency to patchy distribution and to recurrence or migration. Examination of the sputum would be of little help, for, while a certain proportion of the patients with rheumatic pneumonitis retain some hemolytic streptococci in the sputum, many healthy persons as carriers also have them. The blood sedimentation rate is high in each.

Clinical Differences Between Rheumatic Pneumonia and Primary Atypical Pneumonia.—Perhaps the best general plan of distinguishing in an individual case would be the deliberate effort to secure additional clinical evidence of nonsuppurative lesions elsewhere in the body, to suggest that the case is one of rheumatic fever or of some other clinical sequel to streptococcic infection. Such evidence would include mild arthritic manifestations, hematuria, epistaxis, purpura, erythema marginatum, encephalitis and electrocardiographic changes or physical signs to indicate cardiac involvement. Since recurrence is common in rheumatic fever, the history of a previous attack might have weight in the making of a decision. The occurrence of a sore throat a few days or weeks preceding the onset of pulmonary symptoms might suggest the likelihood of a rheumatic type of involvement in the lungs, but direct inquiry may be needed to obtain such a part of the history.

Laboratory Tests.—Two procedures of possible merit are worth suggesting. In many cases of primary atypical pneumonia there is a high titer of cold agglutinins in the serum.[20] This is not described in rheumatic fever. In most cases of acute rheumatic fever there is a rise in antifibrinolysin and antistreptolysin in the blood.[21] Procedures to determine the presence of these substances might prove useful in this particular diagnostic problem.

SUMMARY

A case of rheumatic fever is presented in which death, due primarily to the pulmonary lesions of this disease, occurred thirty days after the onset of acute pharyngitis and fifteen days after the onset of rheumatic pain. Pathologic changes in the lungs and kidneys are described in detail.

The tissue lesion in rheumatic pneumonitis is interpreted as the same as that sometimes occurring in many organs as a nonsuppurative

20. Peterson, O. L.; Ham, T. H., and Finland, M.: Cold Agglutinis (Autohemagglutinins) in Primary Atypical Pneumonias, Science **97**:167 (Feb. 12) 1943. Humphrey, A. A.: Cold Hemagglutination Test in Diagnosis of Primary Atypical Pneumonia, U. S. Nav. M. Bull. **43**:1117-1127 (Dec.) 1944.

21. Boisvert, P. L.: The Streptococcal Antifibrinolysin Test in Clinical Use. J. Clin. Investigation **19**:65-74 (Jan.) 1940. Bunim, J. J., and McEwen, C.: The Antistreptolysin Titer in Rheumatic Fever, Arthritis and Other Disease, ibid. **19**: 75-82 (Jan.) 1940.

sequel to infection with a hemolytic streptococcus, whether or not the disease is expressed clinically with rheumatism. Clinical syndromes caused by such lesions, depending on the organ predominantly involved, may be called acute hemorrhagic nephritis, acute rheumatic fever, acute encephalitis (chorea) or one or another of several other clinical conditions not usually named as if specific diseases.

The similarity between the pathologic anatomy of rheumatic pneumonitis and of so-called primary atypical pneumonia is pointed out, and reasons are given for suspecting that in some cases rheumatic pneumonitis is being mistakenly called primary atypical pneumonia. Means for differentiating them clinically are briefly indicated.

DANGER OF INTRAVENOUS INJECTION OF PROTEIN SOLUTIONS AFTER SUDDEN LOSS OF RENAL TISSUE

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IN cases of shock there may be a sudden loss of effective renal tissue, because for a time the kidney does not get enough blood; more sustained deprivation sometimes occurs after transfusion reactions; there are instances of anatomic as well as functional loss, as when part of the kidney is destroyed by shell fragments, and in glomerular nephritis and symmetric necrosis of the cortex the majority of the nephrons in a short space of time may become functionless and many may be irrevocably destroyed. For each of these situations there is a specific treatment dependent on knowledge of the causative mechanism, but in all, except the most transitory instances of functional loss, we believe that the work demanded from the remaining renal tissue should be reduced. The work of the kidney consists almost wholly in the reabsorption of water from a concentrated solution of urea in the tubules into a relatively dilute solution of urea in the blood. Rest is achieved when a diet that induces a low rate of urea excretion is given and when enough water is taken to keep the urine dilute. Rest is needed when accident or disease suddenly reduces the size of the kidney, because the enzyme systems that transfer water against osmotic pressure are limited in quantity and capacity. The remaining still functioning remnant of kidney then works at top speed, but if rest is not given one finds the signs of "renal failure" appearing in the form of a rapidly rising concentration of nitrogenous metabolites in the blood, and when the overload of work continues there follow proteinuria, cylindruria, anemia, hypertension and finally death in uremia.[1]

A sudden loss of renal tissue, the essential feature of the general situation which we are discussing, can be experimentally reproduced by removing three quarters of the total kidney.

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The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Stanford University.

1. Addis, T.: The Osmotic Work of the Kidney and the Treatment of Glomerular Nephritis, Tr. A. Am. Physicians **55**:223, 1940.

We chose thirty day old rats as subjects because they are more sensitive than older rats to a sudden reduction in the number of nephrons.[2] Eighty-six males were selected from the colony. They had been living on a diet which contained 17 per cent of protein. After one kidney and half the remaining kidney had been excised, the rats were divided into four groups. The first group was given no protein, the second 22.6 per cent and the third 64.1 per cent of protein in the form of lactalbumin. The substrate of all the diets was a starch-lard mixture enriched with ample quantities of vitamins and minerals. Since the variation in protein concentration was obtained by replacing starch with lactalbumin, all these diets were approximately isocaloric. Water was given ad libitum.

The mortality rates during the seven days after operation are given in table 1. These rats died forty-eight hours or more after the operation. We proved that uremia was the cause of death by measuring the urea concentration in the tissues of those which had only recently died.

TABLE 1.—*Death Rate from Uremia, Determined by the Demand for Work Imposed by an Increasing Protein Consumption After Removal of Three Fourths of Kidneys*

Protein, Gm. per Day	Number of Rats	Died in Uremia	Per Cent Mortality
0.00	10	0	0
1.67	15	2	13
2.38	49	21	43

2. After a large loss of renal tissue young rats are more likely than old rats to die of uremia. We think that this is because the younger the rat the greater is the food protein consumption per unit of body size (MacKay, E. M., and MacKay, L. L.: Age and the Effect of Unusual Diets, J. Biol. Chem. **86**:765 [April] 1930). Young rats certainly do not die because their restoration of lost renal tissue is slower (MacKay, L. L.; MacKay, E. M., and Addis, T.: The Effect of Various Factors on the Degree of Compensatory Hypertrophy After Unilateral Nephrectomy, J. Clin. Investigation **1**:576 [Aug.] 1925) or because their vascular system is less able to adapt itself to sudden change. In both these respects 30 day old rats are more capable than 300 day old rats. There is thus an interesting divergence in the effect of age when one compares mortality rates in the uremia following a high protein consumption after partial nephrectomy and the uremia that follows ligation of the vena cava (Addis, T., and Raulston, B. O.: A Reversible Form of Experimental Uremia, Tr. A. Am. Physicians **45**:318, 1930). In older rats death due to uremia, after 75 per cent of the kidney has been removed, is not common under any conditions. The reverse is true when the vena cava is tied above the entrance into the renal veins. Ninety per cent of the old rats die of uremia, while all the young ones survive (Addis, T., and Lew, W.: Age and the Rate of Venous Enlargement Under Increased Venous Pressure, Proc. Soc. Exper. Biol. & Med. **42**:602 [Nov.] 1939). In this case life or death depends primarily on the rate at which there is an enlargement of venous channels through which blood from the kidney can pass from the closed vena cava into veins that run up the abdominal wall and reach the heart above the occlusion. This is a situation that tests the adaptability of the venous system, and in this capacity young rats are clearly superior.

In every case we found more than 500 mg. of urea per hundred grams of tissue. The rate of death in uremia varied with the amount of protein consumed: no deaths after no protein, 13 per cent after 1.67 Gm. and 43 per cent after 2.38 Gm. of protein a day. The protein taken was lactalbumin, but the mortality was not a consequence of any deleterious effect of this particular protein. That is shown by another exactly similar experiment on 30 day old rats which were given 86 per cent casein instead of 86 per cent lactalbumin. The mortality rate was 47 per cent.

On the sixth day after the operation the survivors were placed in special cages, in which they were given free access to their respective diets while the urine was collected on blotting paper. At the end of the twenty-four hour period and seven days after the operation, urine was collected directly from the bladder for determinations of the urea concentration in the urine. The rats were then anesthetized with ether; blood was collected, and measurements of weights of organs were made.[3]

TABLE 2.—*Effect of Increasing Demand for Work Through Increasing Protein Consumption on Kidneys Reduced to Quarter of Original Size Seven Days Before Measurements Were Made*

Group	Protein, Gm. per Day	Changes of Body Weight, per Cent of Original Weight	Kidney Protein Corrected for Body Weight, Mg.*	Urea Excretion, Mg. per 24 Hr.	Serum Urea Concentration, Mg. per 100 Cc.	Urea Clearance, Cc. per 24 Hr.	Urea Work, Calories per 24 Hr.
First.....	0.00	−22	34	42	57	74	0.8
Second.....	1.67	+ 5	37	102	65	157	2.5
Third.....	2.38	−33	42	402	274	147	6.0

* The weights of kidney protein were corrected for the differences in body weight by deriving the amounts to be expected in a 50 Gm. rat by multiplying the observed amounts by $\frac{50^{0.7}}{BW^{0.7}}$.[3] This particular method of correction contributes to the precision of the results, but qualitatively similar conclusions are obtained even when such simple but inaccurate expressions as the number of milligrams of kidney protein per hundred grams of body weight are used.

The results are given in table 2. On comparing the three groups in table 2, it was at once apparent that the rats in the third group, which had eaten the most protein, were all sick. In a week they had lost 33 per cent of their original body weight, although, when we measured their food consumption on the last day, they were taking an adequate number of calories. Their miserable state arose because they were dying of uremia. The 274 mg. of urea per hundred cubic centimeters that we found in their serum was only part of a more general store of retained metabolites. Thus, the creatinine concentration had risen to 4.02 mg. per hundred cubic centimeters, an extremely high level for rats. After the ingestion of 86 per cent of casein, due

3. Walter, F., and Addis, T.: Organ Work and Organ Weight, J. Exper. Med. **69**:467 (March) 1939.

to which the death rate was 47 per cent, the serum urea concentration of the survivors was 320 mg. per hundred cubic centimeters. It is evident that under these conditions the consumption of even the usual amount of protein may induce renal failure.

At first glance it may seem curious that we describe the situation found in the third group as one of "renal failure" when table 2 shows that the kidneys of the animals in this group succeeded in excreting almost ten times as much urea as those of the first group; it may seem perverse to ascribe this failure to an incapacity to do osmotic work when they actually did seven and a half times as much work as the kidneys which we say were successful, and paradoxic to designate as "insufficient" those that cleared twice as much urea as those of the first group. These failing kidneys constructed more new renal tissue than those of the other groups; hence, in the end they were larger and more capable than the others and were equally devoid of any sign of structural defect. But this difficulty arises only because of the natural but erroneous tendency to regard the kidney as a more or less autonomous organ. One is inclined to think of it abstractly in separation from the body, as though it were an organ like the eyes or ears, which, though proportioned to the rest of the body, are, in the main, fixed and given through inheritance. In the kidney, however, there is no approach to such autonomy. Absolute significance cannot be attached to isolated measurements of the structure or function of the kidney. Their meaning lies in their relation to the amount of work that has been imposed. Thus, if one asks what size of kidney is proper for a rat with a body weight of 150 Gm. one finds kidneys whose average weights vary from each other by as much as 66 per cent. It is only through the constant ingestion of a diet that induces some uniformity in osmotic work that there is an approach to the usual degree of constancy that exists between a part and the whole of the body. If the blood urea concentration is taken as a measure of function and we are asked what variation in the level of concentration was to be expected in rats with entirely normal kidneys, we should have to say that we had observed concentrations that varied all the way from 5 to 500 mg. per hundred cubic centimeters. Consequently, the figures in table 2 have to be interpreted in the light of the demand for work from the kidney that was left. Since the number of nephrons had been reduced to a quarter of their original number, the remaining nephrons in each group were called on to do four times as much work as before. Then we went on to vary the demand for work by changing the consumption of protein, and we found that as the demand increased there was an increase in the rate of urea excretion and an acceleration in the rate of formation of new renal tissue and that the amount of work actually done was increased. But the remaining

fragments from which most work was demanded did not grow fast enough, and the work done was inadequate to the demand; hence, uremia supervened, and many died. It was a real failure, but it was relative, not absolute.

From these experiments we must conclude that in young rats suddenly deprived of most of their kidneys even a moderate consumption of protein may induce renal failure and death. Since we know of no evidence that the kidney of a man is fundamentally different from that of a rat because a man's kidney works in the same way and fails in the same way, the amount of protein given to men who have suffered a sudden and serious loss of renal tissue becomes a matter of real concern. If one considers first the situation in which the loss is traumatic and accompanied with shock, the first therapeutic requirement is the reconstitution of a normal circulation. The nature of any protein that may be injected for this purpose is important, because

TABLE 3.—*Urea Excretion (in Milligrams per Twenty-Four Hours) After 0.85 Per Cent NaCl and Injections of Protein*

Day	Injections				
	NaCl Solution	Gelatin	Horse Serum	Bovine Albumin	Rat Serum
First	114	190	173	118	163
Second	63	154	100	70	47
Third	69	180	126	94	76
Fourth	63	147	88	78	40
Fifth	57	142	110	85	67
Sixth	57	139	81	75	45
Seventh	48	179	126	84	64
Totals	471	1,131	804	604	502

some proteins induce a considerable increase in urea excretion and thus increase the work required from the remaining fragment of kidney. In table 3 is given the average daily rate of urea excretion of a group of 15 rats with a body weight of 150 Gm. which at the beginning of the first, third, fifth and seventh days of the period of observation received an intraperitoneal injection of 5 cc. of 0.85 per cent sodium chloride solution per hundred square centimeters of body surface, a quantity corresponding to 900 cc. given to a man of 70 Kg. when estimated on the basis of body surface. This group received adequate calories but no protein because they were kept on 35 per cent dextrose in 0.4 per cent sodium chloride solution with added B vitamins. This is the control for other groups of 15 rats with a body weight of 150 Gm. kept on the same dextrose solution but given the same volume of 6 per cent protein solutions in the form of gelatin, horse serum, bovine albumin and rat serum.

Table 3 shows that the injection of certain proteins leads to greater increase in urea excretion than injection of others and that rat serum gives

the least increase. But it should be noted that on the days of injection even rat serum induces a 30 per cent increase over the control group. This raises the question as to how much increased urea excretion may follow the injection of human plasma into men. In our experiments on rats the protein starvation favored the utilization of the injected protein for the satisfaction of anabolic needs, and a large part was, in fact, so used. We have shown that rats can increase the total quantity of protein in their organs and tissues when intraperitoneally injected horse serum is their only source of material for the building of new protein.[4] But plasma and albumin often have to be given to men under conditions that are much less favorable for protein synthesis. All blood proteins are inadequate, and under the best conditions some loss of urea must be anticipated. When one injects 1 liter of whole blood, one gives approximately 167 Gm. of protein. If it contains 400 Gm. of red blood cells, which contain 30 per cent of protein, one gives 120 Gm., and if there is 670 Gm. of plasma one adds 47 Gm., a total of 167 Gm. When patients who have suffered a serious loss of renal tissue are given multiple injections of whole blood and plasma, as not infrequentiy happens, there may be danger of reproducing the conditions exemplified in table 1. To restore the circulation without imposing work on the kidney there is need in certain clinical situations for a purely carbohydrate substitute for blood plasma that is efficient and safe.

SUMMARY

1. After removal of three quarters of the total renal tissue from young rats there were no deaths when no protein was taken, but as the amounts of protein consumed increased there was an increasing number of deaths in uremia.

2. In the survivors there were no signs of renal failure when no protein was taken, but as the consumption of protein increased the concentrations of urea and creatinine in the serum rose toward uremic levels, although at the same time the rates of urea excretion, of urea clearance, of work accomplished and of new renal tissue constructed were all augmented. This was, therefore, not an absolute renal failure but one that was a failure only in relation to the demand imposed.

3. An increased demand for work from the kidney is imposed by the parenteral injection of any protein to a degree that varies with its nature and with the conditions under which it is administered.

4. Addis, T.; Lee, D. D.; Lew, W., and Poo, L. J.: The Utilization of Parenterally Administered Horse Serum by the Rat, Am. J. Physiol. **128:** 544 (Feb.) 1940.

SULFADIAZINE AND PENICILLIN FOR HEMOLYTIC STREPTOCOCCUS INFECTIONS OF THE UPPER RESPIRATORY TRACT

An Evaluation in Tonsillitis, Nasopharyngitis and Scarlet Fever

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ACUTE infections of the upper respiratory tract due to hemolytic streptococci, while constituting an important health problem in a civilian population, become accentuated during the time of war. This applies particularly to groups of military personnel during the early training period. Several reports have recorded attempts to control hemolytic streptococcus infections in military personnel, and the efforts have not been without some success.[1] The use of the sulfonamide compounds in the treatment of streptococcic infections of the upper respiratory tract has resulted in conflicting reports concerning the effectiveness of these drugs.[2] Until the present investigation was

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This investigation was carried out during a field study by the Commission on Hemolytic Streptococcal Infections, Board for the Investigation of Epidemic Diseases, United States Army.

The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for investigations recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council.

1. Holbrook, W. P.: The Army Air Forces Rheumatic Fever Control Program, J. A. M. A. **126**:84 (Sept. 9) 1944. Coburn, A. F.: The Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine Prophylaxis in the U. S. Navy, ibid. **126**:88 (Sept. 9) 1944. Robertson, O. H.; Hamburger, M., Jr; Loosli, C. G.; Puck, T. T.; Lemon, M. M., and Wise, H.: A Study of the Nature and Control of Air-Borne Infection in Army Camps, ibid. **126**:993 (Dec. 16) 1944.

2. Rhoads, P. S., and Afremow, M. L.: Sulfanilamide in the Treatment of Sore Throat Due to Hemolytic Streptococci, with Controls, J. A. M. A. **114**:942 (March 16) 1940. Freis, E. D.: The Treatment of Tonsillitis with Small Doses of Sulfonamides, ibid. **126**:93 (Sept. 9) 1944.

initiated and completed, no well controlled studies of penicillin in the therapy of infections of the upper respiratory tract, including scarlet fever, had appeared. Plummer and colleagues [3] have recorded the results of penicillin therapy in 28 cases of acute pharyngitis-tonsillitis due to group A hemolytic streptococci. No patients with scarlet fever were treated. There were 6 control patients who did not receive any specific therapy. The authors called attention to the prompt improvement in patients following the intermittent, intramuscular injections of penicillin. But clinical relapses occurred in subjects treated for less than four days, and these relapses coincided with the reappearance of hemolytic streptococci in the nasopharynx. In none of the treated patients did acute rheumatic fever develop.

The purpose of this report is to detail an evaluation of sulfadiazine and, especially, penicillin in the treatment of hemolytic streptococcus infections, such as nasopharyngitis, tonsillitis and scarlet fever. In the initiation of this investigation, three primary objectives were kept in mind: first, to determine whether either sulfadiazine or penicillin shortened the clinical course of a given infection; second, to ascertain whether the number of complications of the disease, including acute rheumatic fever, was reduced by this specific therapy, and, third, to decide whether the treatment was associated with a prompt eradication of hemolytic streptococci from the nasopharynx.

METHODS OF STUDY

Clinical Material.—A total of 210 young men were observed in one training area between December 1943 and May 1944. This included a control group of 102 patients, who did not receive either sulfadiazine or penicillin, 95 patients who were given penicillin or penicillin and sulfadiazine and 19 patients to whom only sulfadiazine was administered. The types of hemolytic streptococcus infections which the patients in the three groups had will be described shortly. All the men were considered ill enough by physicians at the dispensary to require hospital care. The majority of patients were seen in the hospital shortly after the onset of their illness. The patients were assigned to special wards for infections of the upper respiratory tract, where they were first examined by the officer on duty. Within twenty-four hours after entry each patient was seen by at least two members of the Commission on Hemolytic Streptococcal Infections. The Commission obtained a history of the illness from each patient and recorded the results of a physical examination on a special form. After bacteriologic studies or outstanding clinical features had determined that a person had an infection of the upper respiratory tract due to hemolytic streptococci, he was transferred to a ward specifically designated for patients with this type of infection. Each of the patients with streptococcic infections was seen and examined by at least two members of the Commission once or twice daily, and clinical notes were made during the patient's stay in the hospital.

3. Plummer, N.; Duerschner, D. R.; Warren, H. D.; Rogliano, F. T., and Sloan, R. A.: Penicillin Therapy in Hemolytic Streptococcic Pharyngitis and Tonsillitis, J. A. M. A. **127**:369 (Feb. 17) 1945.

Usually the patients did not receive specific therapy until precise bacteriologic data were available. In preliminary treatment the administration of any antipyretics was avoided, and the discomfort of the patients was relieved with barbiturates, codeine sulfate and irrigation of the throat with hot saline solution.

All the patients were arbitrarily divided into three clinical groups. A patient was considered to have tonsillitis when there was definite objective evidence of redness, edema, swelling and exudate involving the tonsillar tissue. Patients with nasopharyngitis constituted a group with and without tonsils but in whom the tonsils did not appear to be primarily involved. Patients with scarlet fever included those who had either tonsillitis or nasopharyngitis but in whom a characteristic dermal rash was present.

Bacteriologic Studies.—Material from the nasopharynx and oropharynx was obtained by swabbing the cavities with cotton-tipped applicators and were then cultured by inoculation of mule blood agar plates. The plates were streaked with a platinum wire loop and incubated aerobically at 37 C. for eighteen to twenty-four hours. The degree of growth of hemolytic streptococci on the plates was quantitated from a minimum growth of 1 plus to a maximum growth of 4 plus. Representative hemolytic colonies were picked and grown on mule blood agar plates and then grown in pure culture in liquid culture mediums. Identification of the group to which the individual strains belonged was determined by the method of Lancefield,[4] while the typing of group A strains was performed according to Lancefield's technic.[5] Materials for cultures were obtained periodically, sometimes daily, from each of the patients during his hospitalization. Grouping and typing of hemolytic streptococci isolated in all cultures were carried out. Arrangements were also made for the majority of the patients to return for a clinical and bacteriologic check-up two to three weeks after discharge from the hospital. Approximately 2,000 cultures of material from the nose and throat were studied during the course of this investigation.

Miscellaneous Laboratory Studies.—In addition to the foregoing bacteriologic investigations, technical assistants in the laboratory of the Commission made total and differential leukocyte counts of the blood before, during and after specific therapy. Serial electrocardiograms were obtained on many of the patients during their period of hospitalization and in some instances after discharge from the hospital. Sedimentation rates of the erythrocytes were determined at intervals on the majority of the patients according to the method of Westergren.[6] Dick tests were applied on a patient's admission to the hospital and then during the stage of convalescence. An analysis of the Dick reaction in these patients constitutes part of a subsequent report. This also applies to the results of several different serologic tests.

Sulfonamide Therapy.—A group of the more seriously ill patients were treated with standardized doses of sulfadiazine by the oral route. An initial dose of 3 Gm. of sulfadiazine was given and then 1 Gm. every four hours until the temperature approached normal. Then 1 Gm. was given every six hours for twenty-four hours. As a prophylactic measure against renal complications from sulfadiazine, the daily

4. Lancefield, R. C.: A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci, J. Exper. Med. **57**:571 (April) 1933.

5. Swift, H. F.; Wilson, A. T., and Lancefield, R. C.: Typing Group A Hemolytic Streptococci by M Precipitin Reactions in Capillary Pipettes, J. Exper. Med. **78**:127 (Aug.) 1943.

6. Westergren, A.: The Technique of the Red Cell Sedimentation Reaction, Am. Rev. Tuberc. **14**:94 (July) 1926.

fluid intake and output were charted for each patient and a minimum output maintained at 1 to 1.5 liters per twenty-four hours. In addition, 2 Gm. of sodium bicarbonate was administered at 8 a.m., 12 noon, 4 p.m., 8 p.m. and 12 midnight. The amount of free sulfadiazine in the blood was determined by the method of Bratton and Marshall.[7]

Penicillin Therapy.—With but few exceptions, all the patients receiving penicillin were assigned to individual rooms in a "penicillin ward," with specially instructed nursing personnel in charge. The sodium salt of penicillin was used. All the solutions of penicillin were freshly prepared by a member of the Commission. As will be pointed out later, a few of the patients received penicillin intravenously by the continuous drip method. Most of the patients were given the material intermittently by the intramuscular route. Individual doses in 1 to 2 cc. of isotonic solution of sodium chloride were injected into the deltoid muscles or the buttocks. The dosage schedules will be detailed shortly. The patients were examined at least twice daily by one member of the Commission and, independently, once a day by a second member. Materials for culture from the nose and throat were obtained daily during the period of therapy and for one week after. A total of 1,139 cultures were examined in patients receiving penicillin.

Penicillin Therapy Combined with Sulfadiazine Therapy.—A group of patients observed in the manner just described were given four intramuscular injections of penicillin, and then, at the time of the last dose of penicillin, therapy with sulfadiazine was started as previously detailed. Treatment with sulfadiazine was continued for four to five days.

Control Group of Patients.—In order to get more precise information concerning the value of specific therapy, a control group of 102 patients having nasopharyngitis or tonsillitis due to hemolytic streptococci were observed. The absence of a large number of patients with scarlet fever militated against a series of untreated controls. The control patients did not receive salicylates, sulfadiazine or penicillin.

It became apparent early in the course of this investigation that the severity of an infection was an important factor in evaluating any therapeutic agent. Therefore, patients falling into either the control or the treated group were divided into three categories. Patients with mild infections had temperatures below 101 F. The throats showed only mild inflammation, slight edema and exudate, and there was a minimum of associated cervical adenitis. There was little systemic reaction to the infections in that the patients ate well and after a good night of sleep were anxious to be out of bed. Patients with moderate infections had temperatures above 101 F. The inflammatory reaction of the throat induced difficulty in swallowing, and all the patients had an associated cervical adenitis. Systemic reactions included headache, dizziness and loss of appetite. The patients had little desire to be out of bed at the end of the first twenty-four hours of hospitalization. Patients with severe infections were febrile, often complaining of chills or chilly sensations. The edema and exudate of the pharynx were pronounced,

7. Bratton, A. C., and Marshall, E. K., Jr.: New Coupling Component for Sulfanilamide Determination, J. Biol. Chem. **128**:537 (May) 1939.

making swallowing of liquids extremely painful. Many of these patients had had emeses and diarrhea. They complained of having severe headaches. There was no inclination to eat. During the first day or two of hospitalization, they were prostrated. The number of patients in each group on the basis of this classification is shown in table 1. The bacteriologic data for 102 patients are presented in table 2. In this particular series of patients, types 19 and 36 of group A hemolytic streptococci appeared to predominate. Although the number of cases is small, no instance of severe tonsillitis or nasopharyngitis was found to be due to other than group A hemolytic streptococci. Rarely was more than one type of group A hemolytic streptococcus isolated from patients with an acute illness. On the other hand, carriers of hemolytic streptococci frequently may harbor two or more types in the pharynx.

In the main, the clinical course of the patients with acute tonsillitis followed a fairly uniform pattern. At the end of four to five days of

TABLE 1.—*Distribution of Control Patients According to Severity of Infections*

	Number of Patients	
Tonsillitis		58
Mild	12	
Moderate	36	
Severe	10	
Nasopharyngitis		44
Mild	18	
Moderate	18	
Severe	8	
Total		102

illness, the temperature approached or became normal. Subjectively, in the cases of more severe illness, the toxemia and sore throat began to abate by the end of forty-eight hours. There was a return of appetite at the same time. Objectively, the edema and exudate began to subside at the end of forty-eight hours of illness. Redness of the throat and adenitis were the last signs to disappear. The redness of the throat frequently persisted after the temperature had remained normal for several days. Likewise, the cervical lymph nodes could not be palpated without some degree of pain being elicited well after the temperature had become normal. The temperature curves and the causative organisms in representative cases of severe tonsillitis are depicted in chart 1. While the majority of patients were enabled to leave the hospital a week after the onset of their illness, they were kept under observation for an additional week in most instances for further bacteriologic and immunologic studies. Suppurative complications were rarely encountered. Cervical adenitis was considered to be a manifestation of acute tonsillitis rather than a complication. Essentially the

TABLE 2.—*Group and Type of Hemolytic Streptococci in Control Patients with Tonsillitis and Nasopharyngitis*

	Types of Group A (Lancefield) Hemolytic Streptococci																			
	3	5	6	9	14	17	18	19	22	26	29	30	36	40	41	44	46	Unable to Type	Group B	Group C	Group G
Tonsillitis																					
Mild	1	..	..	..	..	..	..	3	1	..	1	..	1	..	1	..	..	2	1	1	..
Moderate	..	..	1	..	1	1	1	5	..	1	..	1	12	..	..	1	..	8	..	2	2
Severe	2	..	..	..	..	1	..	2	..	..	..	..	3	..	..	2	..	..	..	..	..
Nasopharyngitis																					
Mild	1	1	..	1	1	..	..	3	..	..	..	2	..	..	1	1	1	2	..	3	1
Moderate	1	..	2	..	1	1	..	2	..	..	..	..	3	1	..	2	1	1	..	2	1
Severe	3	..	..	..	..	..	..	2	..	..	..	..	..	..	..	1	..	2	..	..	..

same clinical course was observed in the patients with severe nasopharyngitis. The temperature curves and the bacteriologic results of typical cases are illustrated in chart 2.

Bacteriologic studies on untreated patients with tonsillitis of all grades of severity showed that two to three weeks after the onset of illness 70 to 75 per cent of the patients still had cultures showing the presence of hemolytic streptococci in the throat, usually of the same

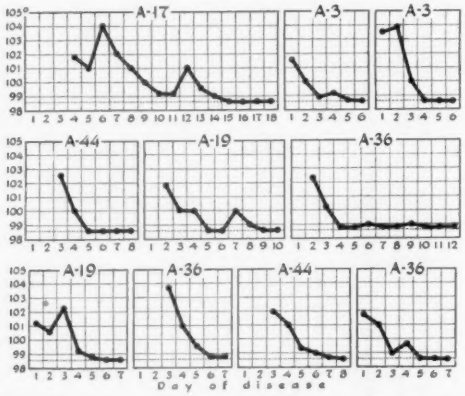

Chart 1.—Composite chart showing temperature curves and types of hemolytic streptococci for 10 patients with severe tonsillitis receiving no specific therapy.

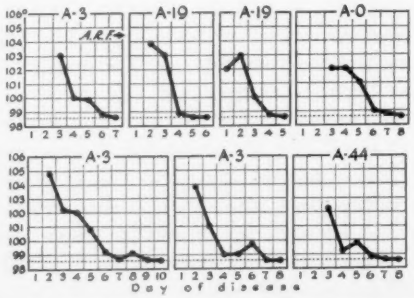

Chart 2.—Composite chart showing temperature curves and types of hemolytic streptococci for 7 patients with severe nasopharyngitis receiving no specific therapy. Note that in 1 patient acute rheumatic fever subsequently developed.

type as isolated on entry to the hospital. This also applied to patients having nasopharyngitis. On the other hand, at the end of this time, there was a pronounced reduction in the incidence of positive cultures of material from the nose. Only approximately 20 to 30 per cent of the

patients continued to have hemolytic streptococci in the nose. Recent evidence accumulated by Hamburger and his group[8] seem to indicate that persons with positive cultures of material from the nose are potentially more dangerous as carriers than those with positive cultures of material from the throat.

EVALUATION OF SULFADIAZINE

The sulfonamide drugs have been used extensively for the treatment of sore throat. The usual method employed is the ingestion of tablets according to various dosage schedules. Another form of therapy is to apply the powder to the pharynx with an atomizer, and, more recently, the use of chewing gum containing a sulfonamide compound has been advocated.

While only 19 patients received sulfadiazine, all were classified as having severe illness. There were 13 with tonsillitis and 6 with nasopharyngitis. Group A hemolytic streptococci were the cause of illness in all cases. Following the dosage schedule previously outlined, the patients received an average of 25 Gm. of sulfadiazine in an average period of five days. In these circumstances, the concentration of free sulfadiazine in the blood varied between 5 and 10 mg. per hundred cubic centimeters. No toxic reactions of any concern were observed. Careful observation of these patients compared with a similar but untreated control group showed that the clinical course of the persons receiving sulfadiazine was altered in one important respect, and that was that the severity of the symptoms abated earlier. The edema of the throat and the exquisite soreness often subsided greatly twelve to eighteen hours after therapy with sulfadiazine was instituted. On the other hand, the duration of the clinical course as a whole was not shortened in the treated group, and therefore the period of hospitalization for the acute illness was the same in the two groups. No conclusions can be drawn concerning the incidence of suppurative complications in the treated group, since complications were uncommon in the untreated patients. It was apparent that sulfadiazine did not reduce the incidence of carriers of hemolytic streptococci. It is of interest that 1 patient having tonsillitis due to group A type 26 hemolytic streptococci was given an initial dose of 3 Gm. of sulfadiazine and then 3 Gm. every three hours, for a total dose of 54 Gm. A 4 plus culture of type 26 hemolytic streptococci was obtained from the throat after therapy had been discontinued.

8. Hamburger, M., Jr.: Studies on the Transmission of Hemolytic Streptococcus Infections: II. Beta Hemolytic Streptococci in the Saliva of Persons with Positive Throat Cultures, J. Infect. Dis. **75**:71 (July-Aug.) 1944.

EVALUATION OF PENICILLIN

A total of 95 patients received penicillin. Six of the patients had acute rheumatic fever, and the results obtained in this group are reported elsewhere.[9] Of the remaining 89 patients, the conditions treated are shown in table 3. It is to be noted that two groups of patients received penicillin and sulfadiazine. It is generally agreed that group A hemolytic streptococci are sensitive to the antibacterial action of penicillin. An attempt was made to determine the minimal doses of penicillin which would alter the clinical course of the disease and also reduce the incidence of postinfection carriers of hemolytic streptococci.

Treatment of Carriers of Hemolytic Streptococci with Penicillin.—An important factor in the dissemination of hemolytic streptococci is the healthy carrier of group A strains and persons recovering from

TABLE 3.—*Types of Conditions in Eighty-Nine Patients Treated with Penicillin or Penicillin and Sulfadiazine*

		Number of Patients
Penicillin		60
Carriers of hemolytic streptococci	10	
Tonsillitis	30	
Nasopharyngitis	9	
Miscellaneous (infections of the upper respiratory tract of nonstreptococcic origin)	8	
Scarlet fever	2	
Erysipelas	1	
Penicillin and sulfadiazine		29
Scarlet fever	13	
Tonsillitis	16	
Total		89

streptococcic infections. Therefore, a group of 10 persons convalescing from various types of group A hemolytic streptococcus infections were treated with penicillin according to different dosage schedules. Pertinent data regarding the treatment of these patients and the results are presented in table 4. The total dose of sodium penicillin varied between 100,000 and 300,000 units. These relatively small doses were selected for evaluation because the use of larger doses would be impractical in most circumstances. The results indicate that the doses used did not eradicate hemolytic streptococci from the throats. The number of patients who had negative cultures of material from the nose is too small from which to draw any conclusions.

Treatment of Tonsillitis Due to Hemolytic Streptococci with Penicillin.—A group of 30 patients with moderate to severe tonsillitis were given varying doses of sodium penicillin, ranging from 75,000 to 1,000,000

9. Rantz, L. A.; Spink, W. W.; Boisvert, P., and Coggeshall, H.: The Treatment of Rheumatic Fever with Penicillin, J. Pediat. **26**:576 (June) 1945.

TABLE 4.—*Effect of Penicillin on "Carrier State" in Patients Convalescing from Group A Hemolytic Streptococcus Infections*

Inital Streptococcic Disease	Total Dose of Penicillin in Units and Method of Administration	Bacteriologic Observations; Group and Type of Hemolytic Streptococci and Quantitative Culture			
		Before Penicillin		After Penicillin	
		Nose	Throat	Nose	Throat
Nasopharyngitis	100,000 as continuous intravenous drip in 10 hr.	Type 0,* 4+	Type 0,* 2+	Negative	Type 0, 1+
Nasopharyngitis	100,000 as continuous intravenous drip in 10 hr.	.....	Type 19, 3+	.....	Type 19, 3+
Tonsillitis	100,000 as continuous intravenous drip in 10 hr.	Type 17, 1+	Type 17, 3+	Negative	Type 17, 3+
Tonsillitis	100,000 as continuous intravenous drip in 10 hr.	Type 36, 2+	Type 36, 3+	Negative	Type 36, 4+
Nasopharyngitis	200,000—25,000 every 6 hr. × 8, intramuscularly	Type 0,* 4+	Type 0,* 3+	Negative	Group G, 1+
Tonsillitis	200,000—25,000 every 6 hr. × 8, intramuscularly	Type 19, 4+	Type 19, 4+	Type 19, 1+	Type 19, 1+
Nasopharyngitis	200,000—25,000 every 4 hr. × 8, intramuscularly	Type 19, 4+	Type 19, 2+	Negative	Type 19, 1+
Convalescent from scarlet fever	300,000—25,000 every 6 hr. × 12, intramuscularly	.....	Type 17, 2+	.....	Group B, 3+
Convalescent from scarlet fever	300,000—25,000 every 6 hr. × 12, intramuscularly	.....	Type 17, 4+	Type 17, 3+	Group G, 3+ Type 17, 1+
Convalescent from scarlet fever	100,000—50,000 every 7 hr. × 2, intramuscularly	Negative	Type 19, 2+	Type 19, 4+	Type 19, 1+

* Type 0 = unable to type.

units. Data pertaining to the doses used, the bacteriologic observations and the clinical results are given in table 5. The effect of the penicillin on the clinical course of the patients was variable with 1 exception. Within eight to twelve hours after the beginning of therapy the majority of patients looked and felt better. This applied to patients who received 25,000 units intramuscularly every four hours for eight

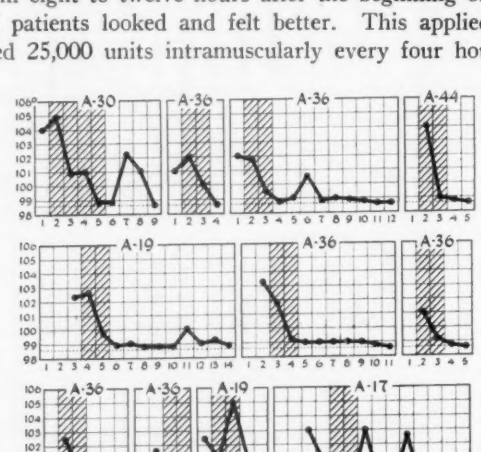

Chart 3.—Composite chart showing temperature curves and types of hemolytic streptococci for 11 patients with severe tonsillitis who received penicillin. Hatched areas indicate periods during which penicillin was given.

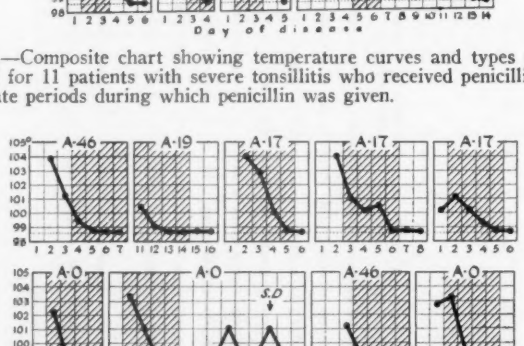

Chart 4.—Composite chart showing temperature curves and types of hemolytic streptococci for 9 patients with severe tonsillitis who received penicillin. Hatched areas indicate periods during which penicillin was given.

doses, for a total of 200,000 units, as well as patients who received a total of 1,000,000 units. With possibly 1 exception, the patients tolerated the penicillin well. In patient 9 a generalized urticaria developed the seventh and eighth days after therapy, when penicillin was discontinued. This was assumed to be due to penicillin, since other possible causes appeared to be ruled out. Charts 3 and 4 present

TABLE 5.—*Effect of Penicillin Administered Intramuscularly on the Clinical Course and Bacteriologic Status of Patients Having*

TABLE 5.—*Effect of Penicillin Administered Intramuscularly on the Clinical Course and Bacteriologic Status of Patients Having Tonsillitis Due to Hemolytic Streptococci*

Total Dose of Penicillin in Units and Method of Administration	Interval Between Initial Treatment and Normal Temperature	Bacteriologic Observations; Group and Type of Hemolytic Streptococci and Quantitative Culture				Comments
		Before Penicillin		After Penicillin		
		Nose	Throat	Nose	Throat	
75,000—15,000 every 4 hr. × 5.....	24 hr.	Negative	Group C, 3+	Negative	Group B, 1+	Within 24 hr. reinfection with group B
150,000—25,000 every 4 hr. × 6.....	48 hr.	Negative	Type 36, 3+	Type 36, 1+	Type 36, 4+	Good response
200,000—25,000 every 4 hr. × 8.....	24 hr.	Negative	Type 36, 4+	Negative	Type 36, 4+	Good response
200,000—25,000 every 4 hr. × 8.....	12 hr.	.....	Group G, 1+	Negative	Negative	Peritonsillar abscess ruptured during therapy
200,000—25,000 every 4 hr. × 8.....	48 hr.	Type 36, 4+	Type 36, 3+	Type 36, 4+	Type 36, 3+	Good response
200,000—25,000 every 4 hr. × 8.....	12 hr.	Type 36, 4+	Type 36, 3+	Type 36, 4+	Type 36, 3+	Clinical relapse
200,000—25,000 every 4 hr. × 8.....	12 hr.	Type 36, 4+	Type 36, 4+	Type 36, 4+	Type 36, 3+	Herpes simplex
200,000—25,000 every 4 hr. × 8.....	48 hr.	Negative	Type 36, 3+	Type 36, 1+	Type 36, 3+	72 hr. after therapy, anorexia and headache
200,000—25,000 every 4 hr. × 8.....	8 days	Negative	Type 36, 4+	Type 0,* 3+	Type 36, 4+	Urticaria 7 and 8 days after therapy; "head cold"
200,000—25,000 every 4 hr. × 8.....	12 hr.	Type 44, 1+	Type 44, 4+	Negative	Type 44, 3+	Good response
300,000—100,000, as intravenous drip; 200,000—25,000 every 4 hr. × 8	4 days	Type 17, 3+	Type 17, 4+	Type 17, 4+	Type 17, 4+	"Head cold" with penicillin; febrile relapse, temperature 101.5 F. day after penicillin therapy discontinued, with rupture of drum membrane due to otitis media; controlled with sulfadiazine
(1) 300,000—25,000 every 4 hr. × 12..... (2) 200,000—25,000 every 4 hr. × 8	24 hr.	Type 19, 4+	Type 19, 4+	Type 36, 3+	Type 36, 3+	Received 12 Gm. sulfadiazine without effect; good response to first course penicillin; reinfection with type 36; good response to second course of penicillin
400,000—50,000 every 4 hr. × 8.....	6 days	Type 17, 4+	Type 17, 4+	Negative	Type 17, 3+	Fair response
400,000—25,000 every 4 hr. × 16.....	6 days	Type 0,* 2+	Type 0,* 1+	Negative	Type 0,* 1+	Slow response
400,000—25,000 every 6 hr. × 16.....	5 days	Type 36, 2+	Type 36, 4+	Negative	Type 36, 3+	Severe clinical relapse 48 hr. after therapy; acute rheumatic fever
400,000—50,000 every 6 hr. × 8.....	24 hr.	Type 0,* 2+	Type 0,* 4+	Negative	Type 0,* 4+	Herpes simplex
400,000—50,000 every 6 hr. × 8.....	13 days	Type 19, 4+	Type 19, 3+	Negative	Type 19, 4+	Fair response
400,000—50,000 every 4 hr. × 4; 25,000 every 6 hr. × 8	7 days	Negative	Type 3, 3+	Negative	Negative	Fair response
450,000—50,000 every 4 hr. × 2; 25,000 every 4 hr. × 4; 15,000 every 4 hr. × 10	5 days	Negative	Type 3, 4+	Negative	Negative	Good response
500,000—25,000 every 4 hr. × 20.....	48 hr.	Negative	Type 46, 3+	Type 46, 1+	Type 46, 1+	Good response
500,000—25,000 every 4 hr. × 20.....	48 hr.	Type 19, 4+	Type 19, 4+	Negative	Negative	Good response
500,000—25,000 every 4 hr. × 20.....	96 hr.	.....	Type 36, 3+	Negative	Negative	Herpes simplex
500,000—25,000 every 4 hr. × 20.....	48 hr.	Negative	Type 0,* 4+	Negative	Negative	Good response
500,000—25,000 every 4 hr. × 20.....	96 hr.	Negative	Type 17, 1+	Negative	Negative	Good response
500,000—25,000 every 4 hr. × 20.....	96 hr.	Negative	Group G, 4+	Negative	Negative	Good response
500,000—25,000 every 4 hr. × 20.....	6 days	Negative	Type 0,* 1+	Negative	Negative	Fever, 7 days after therapy; acute rheumatic fever
1,000,000—50,000 every 4 hr. × 20.....	72 hr.	Negative	Type 0,* 4+	Negative	Type 0,* 3+	5 days after therapy, temperature 101 F.; recovery after sulfadiazine
1,000,000—50,000 every 4 hr. × 20.....	24 hr.	Type 0,* 4+	Type 0,* 3+	Type 0,* 3+	Type 0,* 4+	Slight clinical relapse
1,000,000—50,000 every 4 hr. × 20.....	24 hr.	Type 19, 4+	Type 19, 4+	Negative	Negative	Good response
1,000,000—50,000 every 4 hr. × 20.....	24 hr.	Type 46, 4+	Type 46, 3+	Negative	Negative	Good response

* Type 0 = unable to type.

composite data for 20 patients who received varying doses of penicillin. If one compares the temperature curves of the untreated control group (chart 1) with the curves of the treated group (chart 3), it is to be noted that there is little difference in the time in which the temperatures become normal. Objectively, the throats of the treated group did not manifest any abrupt clearing of the exudate and redness when compared with the control group. The edema of the pharynx and tonsils and the cervical adenitis of patients receiving penicillin did appear to recede more rapidly than that of those in the untreated group. The outstanding difference between the two groups as already cited was that the treated persons felt better sooner than the patients who did not receive penicillin.

There were 6 persons (patients 6, 8, 12, 22, 23 and 24) who had clinical relapses following the cessation of therapy with penicillin. In 5 of the 6 patients, this was associated with a bacteriologic relapse. The relapses did not appear to be related to the total dose of penicillin administered. The significance of these postpenicillin relapses will be commented on shortly. Acute rheumatic fever developed in 2 persons (patients 12 and 22) as a sequel to their streptococcic infections.

The effect of penicillin on the presence of hemolytic streptococci in the noses and throats of these patients is of considerable significance. Materials for culture from the nose and throat were obtained from the patients every day during the course of treatment and for at least one week thereafter. When a total dose of 200,000 units was administered, hemolytic streptococci were frequently absent from cultures during the period of therapy. However, with this dose, streptococci of the same type usually reappeared in the cultures immediately after the cessation of therapy. When a total dose of 400,000 to 500,000 units was given, streptococci again were absent from cultures. After treatment was discontinued the cultures of material from the throat became positive but the cultures of material from the nose remained free of streptococci. In other words, it would appear that such doses eradicated streptococci from the nose but not from the throat. When 500,000 to 1,000,000 units of penicillin were administered, the majority of patients showed an absence of hemolytic streptococci in the nose and throat during and after therapy. Nevertheless, in 2 patients (patients 23 and 24) who received 1,000,000 units, group A hemolytic streptococci persisted in the nose and throat of 1 and in the throat of the other after therapy had been discontinued.

The advantages and disadvantages of therapy with penicillin may be further illustrated by a discussion of the following cases.

CASE 1.—A 32 year old white man entered the station hospital on Feb. 15, 1944. Two days previously he had had chills, fever, severe sore throat, headache and generalized malaise. On entry, the tonsils were massively enlarged, meeting

in the midline, and greatly inflamed, with exudate present in the crypts. He was seriously ill, and on the second day in the hospital therapy with sulfadiazine was started. The patient received a total of 12 Gm. in three days. The level of free sulfadiazine in the blood was 10.44 mg. per hundred cubic centimeters. This treatment was without demonstrable benefit. A consultant stated that the patient had an early peritonsillar abscess on the left associated with pronounced left cervical adenitis. At this time he was given 25,000 units of sodium penicillin intramuscularly every four hours for twelve doses, or a total of 300,000 units in three days.

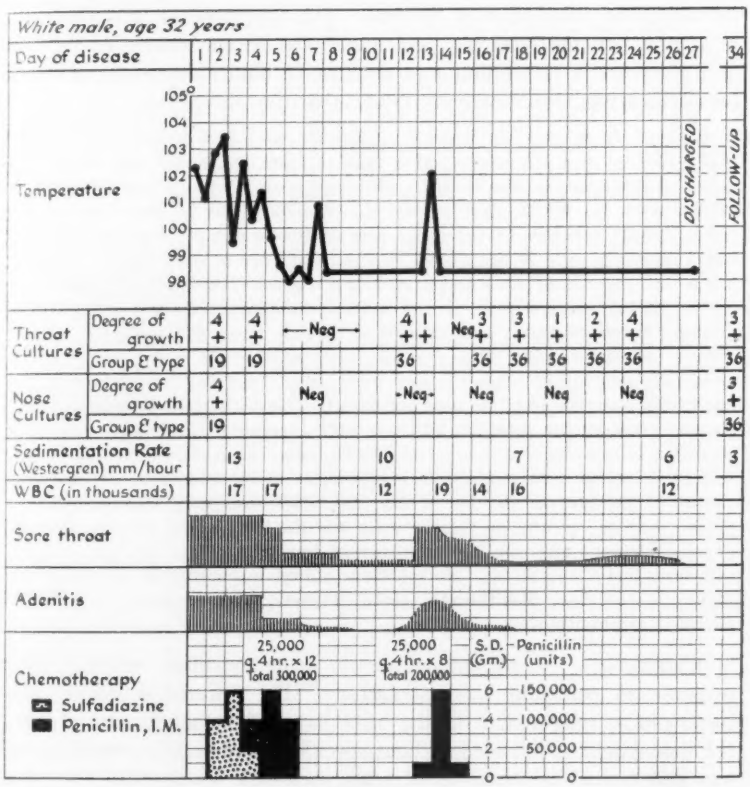

Chart 5.—Effect of penicillin on the clinical course of a severe tonsillitis. Note that sulfadiazine failed to affect the clinical course but a prompt response with penicillin was obtained.

This procedure resulted in prompt improvement. On the third day of treatment there was no adenitis and the peritonsillar swelling had subsided. The day after penicillin had been discontinued the patient had a febrile reaction of 101.6 F. but no other complaints. Seven days after therapy with penicillin he had a remission of his symptoms. This probably represented a hospital reinfection, since on the initial cultures were group A type 19 streptococci and this relapse was associated with

group A type 36 organisms. Penicillin was again administered intramuscularly in doses of 25,000 units every four hours for eight doses, or a total of 200,000 units. There was prompt improvement, but the type 36 streptococci were only temporarily eradicated from the throat. The patient's clinical course is illustrated in chart 5.

Comment: This patient was definitely benefited by penicillin on two occasions. Although the first course of penicillin resulted in prompt improvement, he had a temporary febrile relapse on the day following the completion of therapy. This phenomenon was observed in several patients receiving penicillin. The second course of therapy was given for a reinfection and resulted in clinical improvement, but hemolytic streptococci were not eradicated from the pharynx.

Case 2.—A 36 year old white man entered the station hospital on Feb. 21, 1944. He had had hoarseness and a nonproductive cough for one week. His illness was mild, and he was afebrile. Although group A type 30 streptococci were isolated from his throat, there existed the possibility that he had a nonstreptococcic, "viral" infection of the upper part of the respiratory tract and that he was a carrier of type 30 organisms. On the ninth day in the hospital he became febrile and generalized aches and pains and a headache developed. The following day he became extremely ill, with a severe sore throat, enlarged and reddened tonsils, pronounced edema and exudate of the left tonsil and moderately severe bilateral cervical adenitis. The next day his condition was worse, with evidence of an early peritonsillar abscess present on the left. Type 36 streptococci were cultured from materials from the nose and throat. This indicated a hospital infection. He was given sodium penicillin intramuscularly, receiving 25,000 units every four hours for sixteen doses, or a total of 400,000 units. Coincident with this therapy there was prompt and progressive improvement in his condition. At the conclusion of therapy, on the fourth day, the throat was only slightly sore, but exudate was still present on the left tonsil and the left cervical adenitis persisted. Forty-eight hours after the discontinuation of penicillin therapy, he had a relapse, with fever and a sore throat. No specific treatment was instituted, and he became afebrile in two days. Subsequently, acute rheumatic fever developed. His clinical course is graphically shown in chart 6.

Comment: The patient had severe acute tonsillitis, but his initial response to penicillin was satisfactory. He suffered a clinical and bacteriologic relapse due to the same type of hemolytic streptococci, but the symptoms subsided without specific therapy. His convalescence was complicated by the onset of acute rheumatic fever.

Case 3.—A 19 year old white youth entered the station hospital because of a sore throat and slight fever of one day's duration. He had an injected pharynx, with enlarged red tonsils having exudate in the follicles. Group C hemolytic streptococci were isolated from the throat. His course was benign, but the day before he left the hospital group A type 17 streptococci were obtained in a culture of material from the throat. On the day of discharge he felt feverish and his throat was sore. The following day he was readmitted to the hospital because of a severe sore throat and a temperature of 102.5 F. The tonsils were extremely enlarged and reddened, and considerable exudate was present on each tonsil. He also had a severe degree of cervical adenitis. Type 17 streptococci were again

found in cultures of material from the throat. On his second day in the hospital he was given 100,000 units of penicillin in 1 liter of isotonic solution of sodium chloride as an intravenous drip. Although his temperature dropped and no hemolytic streptococci were obtained from a culture of material from the throat, his general condition had not changed much for the better. Shortly after receiving

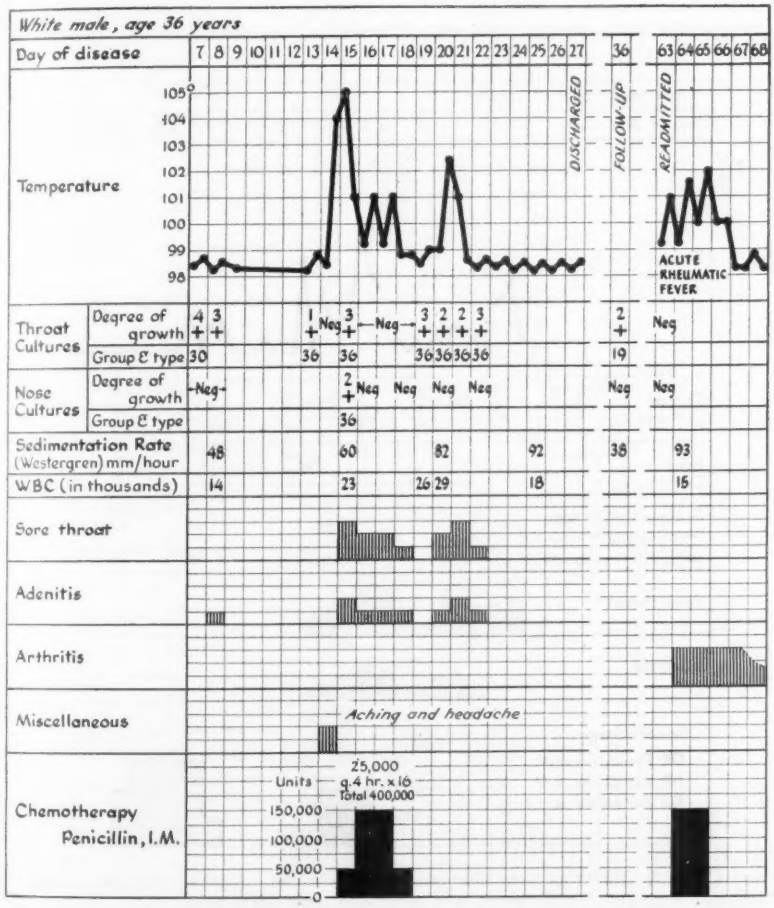

Chart 6.—Effect of penicillin on clinical course of severe tonsillitis. Note the bacteriologic and clinical relapse after 400,000 units had been given. Acute rheumatic fever developed in the patient, which was controlled with a salicylate.

the penicillin, he complained of pain in the right ear; examination revealed a red tympanic membrane but not one that was bulging. That evening he had a severe sore throat; he was unable to swallow, and his ear ached considerably. On the following day the ear had stopped aching, the tonsils did not appear so edematous.

his throat was still sore and the adenitis was less pronounced, but the exudate on the tonsils was just as prominent. He was then given an additional 200,000 units of penicillin intramuscularly in seven divided doses. After the therapy, he felt much better. He was afebrile, the adenitis was diminished and the edema, redness and exudate of the tonsils had receded about 50 per cent. He continued to improve, but on the day following the discontinuation of penicillin he complained of the symptoms of a "head cold." Simultaneously, type 17 hemolytic streptococci reappeared in his pharynx. Six days following therapy with penicillin, his tonsils

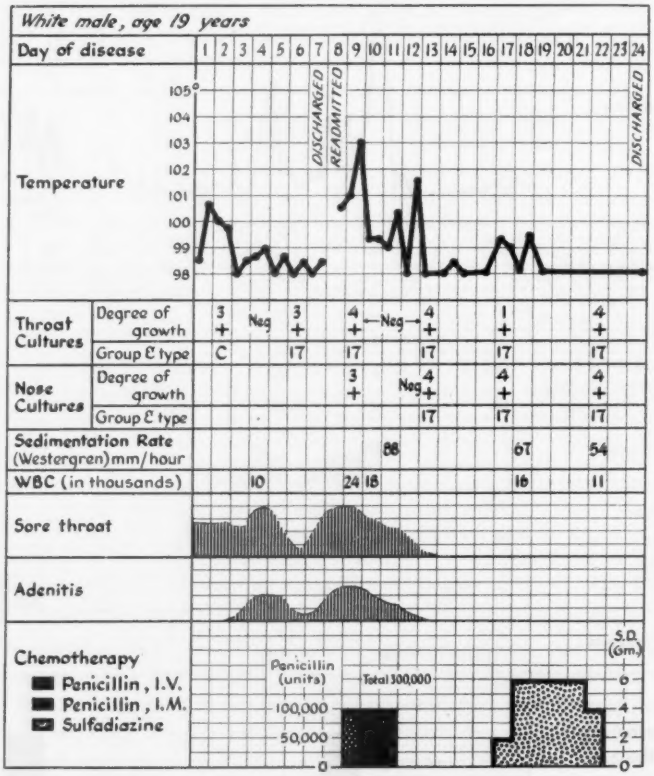

Chart 7.—Effect of penicillin on severe tonsillitis. Clinical and bacteriologic relapse occurred. Otitis media was controlled with sulfadiazine.

were decidedly injected, with a reappearance of exudate and edema. He also complained of a throbbing pain in his right ear, and the tympanic membrane was reddened but not bulging. During the night the membrane of his ear drum ruptured spontaneously, and a serosanguineous discharge was present. Group G streptococci were cultured from this material. He was then given sulfadiazine for the next five days, receiving a total of 30 Gm. Under this regimen, the aural discharge disappeared, and he made an uneventful recovery. When he left the

hospital, group A type 17 streptococci were still present in the nose and throat. Chart 7 illustrates the clinical course and the treatment of this patient.

Comment: This patient had clinical relapses after each of two courses of penicillin. Otitis media was not completely controlled with penicillin, but it abated after spontaneous drainage and the use of

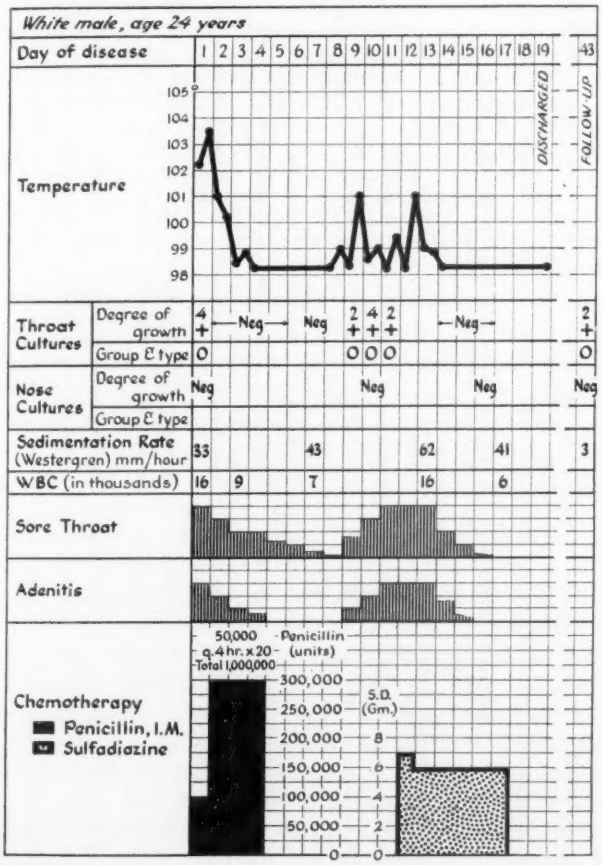

Chart 8.—Effect of 1,000,000 units on severe tonsillitis. Note the clinical and bacteriologic relapse, which subsided when sulfadiazine was administered. 0 indicates that we were unable to type the organisms.

sulfadiazine. The patient also had a bacteriologic relapse with type 17 streptococci.

Case 4.—A 24 year old white man entered the station hospital on March 16, 1944. The day before entry he had an onset of chills, headache and severe malaise.

TABLE 6.—*Effect of Penicillin Administered Intramuscularly on the Clinical Course and Bacteriologic Status of Patients Having Nasopharyngitis Due to Hemolytic Streptococci*

Total Dose of Penicillin in Units, and Method of Administration	Interval Between Initial Treatment and Normal Temperature	Bacteriologic Observations; Group and Type of Hemolytic Streptococci and Quantitative Culture				Comments
		Before Penicillin		After Penicillin		
		Nose	Throat	Nose	Throat	
200,000—25,000 every 4 hr. × 8.....	12 days	Type 0,* 2+	Type 0,* 3+	Type 0,* 1+	Type 0,* 4+	Temperature 102 F., 5h day after therapy
200,000—25,000 every 4 hr. × 8.....	24 hr.	Type 36, 3+	Type 36, 3+	Negative	Type 36, 3+	Fever 24 hr. after therapy, persisting for 17 days; responded to sulfadiazine; then atypical pneumonia
200,000—50,000 every 6 hr. × 4.....	48 hr.	Negative	Type 0,* 3+	Negative	Negative	Good response
300,000—37,500 every 4 hr. × 8.....	24 hr.	Negative	Type 0,* 2+	Negative	Type 0,* 3+	48 hr. after therapy, temperature 101.4 F.; normal in 96 hr.
400,000—50,000 every 4 hr. × 8.....	36 hr.	Type 13 and 28, 2+	Type 13 and 28, 3+	Negative	Type 13 and 28, 3+	48 hr. after therapy, temperature 99.2 F., with slight adenitis
500,000—25,000 every 4 hr. × 20.....	72 hr.	Type 12, 3+	Type 12, 3+	Negative	Type 12, 3+	Fair response
500,000—25,000 every 4 hr. × 20.....	24 hr.	Negative	Group B, 3+	Negative	Type 0,* 3+	Clinical relapse due to reinfection with another type
500,000—25,000 every 4 hr. × 20.....	48 hr.	Type 46, 3+	Type 46, 4+	Negative	Negative	Good response
1,000,000—50,000 every 4 hr. × 20.....	24 hr.	Type 46, 3+	Type 46, 3+	Negative	Type 46, 3+	72 hr. after therapy temperature 102 F.

* Type 0 = unable to type.

On entry, he appeared rather toxic. His pharynx and tonsils were extremely reddened and edematous, with considerable exudate on the left tonsil. A severe bilateral cervical adenitis was present. While group A streptococci were obtained from a culture of material from the throat, typing of this strain was unsuccessful. He was given 1,000,000 units of penicillin intramuscularly in doses of 50,000 units administered every four hours twenty times. On the second day of therapy he felt much better, although his throat and the adenitis appeared essentially the same. However, from then on there was subjective and objective improvement. Three days after the cessation of therapy his pharynx and tonsils appeared normal and he had no complaints. Five days after therapy he had fever, with headache, sore throat and redness and edema of the throat. He also had a bacteriologic relapse. He was then given a total of 19 Gm. of sulfadiazine in a period of three days, which was associated with progressive improvement. Hemolytic streptococci disappeared from the throat while sulfadiazine was being administered. Chart 8 illustrates the clinical course of this patient.

Comment: A patient with severe tonsillitis was given 1,000,000 units of penicillin, which was associated with progressive improvement. However, five days after the completion of therapy, he had a clinical relapse and sulfadiazine was administered. He then made an uneventful recovery.

Treatment of Nasopharyngitis Due to Hemolytic Streptococci with Penicillin.—A group of 9 patients having a severe form of nasopharyngitis due to hemolytic streptococci were treated with intramuscular injections of sodium penicillin. The total doses of penicillin varied between 200,000 and 1,000,000 units. The initial clinical results obtained in this group were essentially the same as those observed in the foregoing patients with tonsillitis. Clinical and bacteriologic data relating to this group of patients are presented in table 6.

While the initial response to penicillin was satisfactory, it is to be noted that 6 of the 9 patients treated had clinical relapses with varying degrees of severity following the discontinuation of therapy with penicillin. In every instance except 1 the clinical relapse was associated with the same type of streptococci which precipitated the original illness. While 8 of the 9 patients had negative cultures of material from the nose when discharged from the hospital, only 2 patients had cultures of material from the throat free of hemolytic streptococci. It is of interest that 1 patient (patient 5) had types 13 and 28 in his nose and throat just before penicillin was administered and after therapy the same two types were present in the culture of material from the throat but absent from that from the nose.

In summing up the advantages and disadvantages of the use of penicillin for tonsillitis and nasopharyngitis of streptococcic origin, one finds the following advantages:

1. The severity of the symptoms appeared to abate more rapidly than did that of the untreated patients or of the group treated with

sulfadiazine. These beneficial effects were observed with as little as 200,000 units given intramuscularly in divided doses.

2. Severe tonsillitis with such complications as early peritonsillar abscess may not respond favorably to sulfadiazine, but desired results may follow the administration of penicillin.

3. Therapy with penicillin was rarely associated with toxic reactions.

The disadvantages of using penicillin for these diseases are as follows:

1. It is necessary to administer the material parenterally in divided doses, which would prove to be impractical in many instances. Penicillin did not prove to be effective in a few cases when a solution of the material was applied locally to the issues with an atomizer at frequent intervals.

2. While doses of 200,000 units provoked a satisfactory clinical response, doses of 500,000 to 1,000,000 units given in divided amounts were necessary before hemolytic streptococci could be considered to be eradicated from the pharynx. Even with these doses, bacteriologic relapses occurred, though during the period of therapy streptococci were absent from cultures of material from the nose and throat. The period over which a total dose of penicillin was administered appeared to be an important factor in eliminating hemolytic streptococci from the pharynx. Thus, multiple small doses given over a period of several days appeared to be more advantageous than the same total dose given in a shorter period. On the other hand, such a procedure was not without considerable discomfort to the patient when as many as twenty intramuscular injections were given.

3. While the initial therapeutic response to penicillin was satisfactory and streptococci were often absent from cultures of material from the nose and throat after the cessation of therapy, several instances of more or less severe clinical relapses were encountered. These relapses were often associated with the reappearance in the throat of the same type of hemolytic streptococci which initiated the illness. Not only did clinical relapses occur, but complications such as otitis media were encountered.

4. Penicillin did not prevent the development of acute rheumatic fever as a sequel to the streptococcic disease for which penicillin was administered.

Treatment of Miscellaneous Infections of the Upper Respiratory Tract of Nonstreptococcic Origin with Penicillin.—During the course of this investigation, a small group of patients with nonstreptococcic infections of the upper respiratory tract were treated with penicillin. These patients were acutely ill when first seen, and the clinical features suggested an infection due to hemolytic streptococci. Therefore, before

the bacteriologic results were known, the patients were given the anticipated benefit of therapy with penicillin. These patients included 3 with tonsillitis and exudate on the tonsils and 4 with nasopharyngitis. Cultures of material from the nose and throat on repeated occasions failed to reveal the presence of hemolytic streptococci. In these circumstances, the clinical effect of penicillin could not be ascertained. Coincident with the administration of 200,000 to 1,000,000 units of penicillin, the patients improved. It is of significance that several of these patients had hoarseness and cervical adenitis was minimal or absent. The latter is uniformly present in patients having tonsillitis and nasopharyngitis of hemolytic streptococcus origin.

One patient with a severe peritonsillar abscess was treated with penicillin. He experienced considerable relief only after spontaneous rupture of the abscess occurred. Cultures of material from the nose and throat obtained before and after therapy failed to reveal the presence of hemolytic streptococci. In fact, aerobic and anaerobic cultures were made with purulent exudate obtained from the site of rupture, and no micro-organisms were recovered. Penicillin did not affect the course of this patient's illness.

Treatment of Erysipelas with Penicillin.—Only 1 patient was treated, and he received 200,000 units. The infection was due to type 44 streptococci. Coincident with therapy begun on the second day of illness, there was progressive improvement. Type 44 streptococci were present in cultures of material from the throat after therapy was completed.

EVALUATION OF PENICILLIN IN COMBINATION WITH SULFADIAZINE

In order to obviate the necessity of giving multiple injections of penicillin for several days, it was decided to give a total amount of 200,000 units of penicillin in divided doses to a group of patients and then to follow this with sulfadiazine. Another reason for considering this therapeutic approach was an attempt to prevent the clinical relapses which were seen after penicillin alone was used. It was noted that although streptococci were not usually eliminated from the throat during or after therapy with sulfadiazine clinical relapses were less frequently encountered. While treatment with penicillin resulted in a more satisfactory initial clinical response and streptococci in the majority of cases were absent from cultures of material from the throat during the period of therapy, the clinical relapses were often associated with the reappearance of streptococci in cultures of material from the throat. The relapses, with a few exceptions, were not severe. The significant observations were fever lasting twenty-four to forty-eight hours, recurrence of a sore throat, reappearance of exudate in some instances and, more commonly, recurrence of edema and redness of the pharynx

and tonsils. That these clinical manifestations were relapses and not reinfections is shown by the fact that the same type of hemolytic streptococci was present in cultures of material from the throat as was found before treatment with penicillin. The significance of these relapses occurring in the group treated with penicillin will be discussed shortly.

Treatment of Tonsillitis with Penicillin Followed by Sulfadiazine.—A group of 14 patients having severe tonsillitis due to group A hemolytic streptococci were first treated with 200,000 units of penicillin, 50,000 units being given intramuscularly every six hours for four doses. At the time of the last injection of penicillin, the patients were given 3 Gm. of sulfadiazine and then 1 Gm. every four hours. The total dose of sulfadiazine, the duration of treatment and the results are shown in table 7.

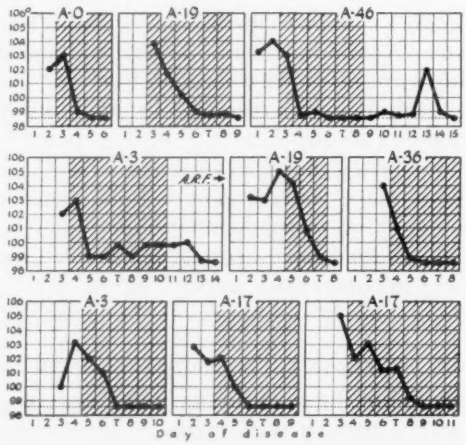

Chart 9.—Composite chart for 9 patients with severe tonsillitis who received 200,000 units of penicillin and then sulfadiazine. Acute rheumatic fever developed in 1 patient. Hatched areas indicate period when penicillin and sulfadiazine were administered. 0 indicates that we were unable to type the organisms.

All the patients tolerated the treatment well except 1 (patient 2), in whom urticaria and hallucinations developed on the second day of therapy with sulfadiazine. It was not known whether this reaction was due to penicillin or to sulfadiazine.

The response of the patients to the treatment was not dramatic, although the severity of the disease appeared to be diminished soon after treatment with penicillin was begun. Chart 9 is a composite chart for 9 patients with severe tonsillitis who received both drugs. The effect of this combined treatment on the streptococci in the nose and throat was of interest in that the majority of the patients had negative cultures while receiving penicillin and sulfadiazine, but when

TABLE 7.—*Effect of Penicillin Administered Intramuscularly and Followed by Sulfadiazine Administered Orally on the Clinical Course and Bacteriologic Status of Patients Having Tonsillitis Due to Hemolytic Streptococci*

Total Dose of Penicillin in Units, and Method of Administration	Total Dose Sulfadiazine	Interval Between Initial Treatment and Normal Temperature	Bacteriologic Observations; Group and Type of Hemolytic Streptococci and Quantitative Culture				Comments
			Before Treatment		After Treatment		
			Nose	Throat	Nose	Throat	
200,000—50,000 every 6 hr. × 4....	33 Gm. 6 days	11 days	.....	.....	Negative	Type 3, 3+	Temperature of 100 F. persistent 8 days after treatment started; reinfection type 46, 10 days after sulfadiazine discontinued; 29 days after sulfadiazine, acute rheumatic fever, with type 30 in throat
200,000—50,000 every 6 hr. × 4....	8 Gm. 2 days	48 hr.	Type 19, 4+	Type 19, 4+	Negative	Negative	Good response; sulfadiazine stopped because of urticaria and hallucinations
200,000—50,000 every 6 hr. × 4....	24 Gm. 5 days	48 hr.	Negative	Type 0,* 1+	Negative	Type 0,* 2+	Good response
200,000—50,000 every 6 hr. × 4....	41 Gm. 7 days	96 hr.	Type 17, 4+	Negative	Negative	Type 46, 1+	Fair response; reinfection with another type
200,000—50,000 every 6 hr × 4....	29 Gm. 5 days	6 days	Negative	Type 3, 3+	Negative	Type 3, 4+	Fair response; "head cold" during therapy
200,000—50,000 every 6 hr. × 4....	27 Gm. 5 days	72 hr.	Type 46, 1+	Type 46, 3+	Negative	Type 46, 4+	5 days after sulfadiazine clinical relapse with temperature 102 F.
200,000—50,000 every 6 hr. × 4....	27 Gm. 5 days	48 hr.	Negative	Type 3, 3+	Negative	Negative	Good response
200,000—50,000 every 6 hr. × 4....	27 Gm. 5 days	6 days	Negative	Type 19, 3+	Type 19, 1+	Type 19, 1+	Fair response
200,000—50,000 every 6 hr. × 4....	20 Gm. 4 days	96 hr.	Negative	Type 36, 4+	Negative	Negative	Fair response
200,000—50,000 every 6 hr. × 4....	25 Gm. 5 days	48 hr.	Type 17, 4+	Type 17, 3+	Negative	Type 17, 3+	Good response; acute rheumatic fever developed
200,000—50,000 every 6 hr. × 4....	27 Gm. 5 days	72 hr.	.....	Type 5, 3+	Negative	Type 5, 4+	Fever and tonsillitis 48 hr. after therapy
200,000—50,000 every 4 hr. × 4....	40 Gm. 7 days	5 days	Type 3, 3+	Negative	Negative	Negative	Peritonsillar abscess ruptured during penicillin therapy; culture of exudate sterile
150,000—25,000 every 4 hr. × 6....	26 Gm. 5 days	96 hr.	Type 5, 4+	Type 5, 3+	Negative	Type 5, 3+	Good response
200,000—50,000 every 8 hr. × 4....	38 Gm. 10 days	14 days	Type 17, 4+	Type 17, 3+	Negative	Type 17, 1+	Otitis media aborted; sinusitis but slightly improved

* Type 0 = unable to type.

therapy was discontinued there was a reappearance of streptococci in the cultures of material from the throat in all the patients except 3. However, only 1 patient had a positive culture of material from the nose when he left the hospital. Two patients (patients 6 and 11) had bacteriologic and clinical relapses after therapy had been discontinued. One patient (patient 1) had a reinfection with another type of hemolytic streptococcus, and a severe form of acute rheumatic fever developed. A second patient (patient 10) had a bacteriologic relapse and acute rheumatic fever developed.

The following 2 cases illustrate the effect of this type of therapy on the disease:

CASE 1.—A 19 year old white youth entered the station hospital on March 22, 1944. The previous day he had an onset of sore throat, fever, chills and vomiting. He appeared extremely toxic, complaining of a severe sore throat and inability to eat. The pharynx was red and edematous, with considerable exudate on both tonsils, and a severe bilateral cervical adenitis was present. Type 19 streptococci were isolated on culture of materials from the nose and throat. He was given penicillin as described and then 25 Gm. of sulfadiazine in five days. The concentration of free sulfadiazine in the blood was 9.6 mg. per hundred cubic centimeters on one occasion and 5.3 mg. at another time. On the second day of treatment the patient appeared much better, though he complained of nasal congestion and felt as if he had a "severe head cold." He continued to improve. On the third day of treatment he had an earache, which promptly subsided with the continuation of therapy. After therapy with sulfadiazine was stopped, cultures of material from the throat, which had been negative for streptococci during therapy, promptly became positive for the same type of streptococci. Although he appeared to be completely recovered, a severe form of acute rheumatic fever subsequently developed. Chart 10 illustrates the clinical course of this patient.

Comment: A patient acutely ill with tonsillitis appeared to make a satisfactory response to penicillin and sulfadiazine. During therapy, cultures of material from the throat remained negative, but they became positive at the conclusion of therapy. Acute rheumatic fever subsequently developed as a sequel to his infection.

CASE 2.—A 19 year old white youth entered the station hospital on March 16, 1944. On the day of entry, headache, fever, sore throat and nonproductive cough developed. The patient appeared extremely toxic. His appetite was poor. The tonsils were noticeably enlarged and reddened, and a moderate amount of exudate covered the surfaces. He had moderate bilateral cervical adenitis. Type 46 streptococci were obtained from the nose and throat on culture. The patient was given 200,000 units of penicillin in amounts of 50,000 units every six hours for four doses. At the same time the last dose of penicillin was administered, sulfadiazine was started, and he received 27 Gm. in five days. The blood level of free sulfadiazine was 7.6 mg. per hundred cubic centimeters. On the second day of therapy, the patient was much improved. The exudate on the tonsils was much less, and the adenitis had diminished in severity. On the fourth day the pharynx appeared normal, there was no adenitis and the patient did not have a sore throat. Eleven days after the beginning of therapy and five days after therapy with sulfa-

diazine had been discontinued, fever and a sore throat developed. Exudate on the tonsils and adenitis reappeared. This relapse subsided without specific therapy. All but 1 culture of material from the throat was negative for hemolytic strep-

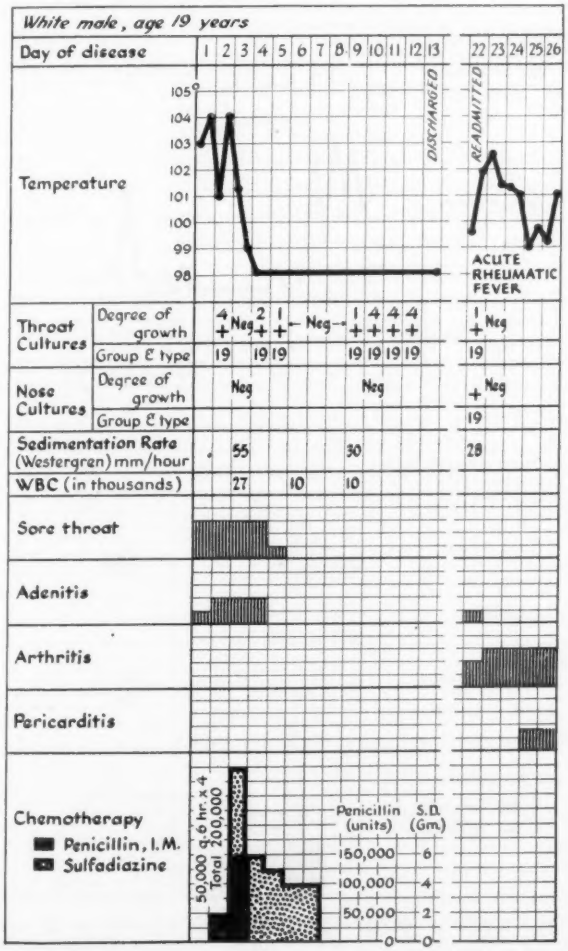

Chart 10.—Effect of 200,000 units of penicillin followed by 25 Gm. of sulfadiazine on the clinical course of severe tonsillitis. Note the bacteriologic relapse and subsequent development of acute rheumatic fever.

tococci during the period when the patient was receiving penicillin and sulfadiazine. There was an immediate bacteriologic relapse, with the same type of streptococci at the cessation of treatment. Chart 11 shows the course of this patient.

Comment: A patient with tonsillitis responded satisfactorily to penicillin and sulfadiazine. Following the cessation of therapy, there was a bacteriologic relapse, which, in turn, was succeeded by a clinical relapse. Spontaneous recovery ensued.

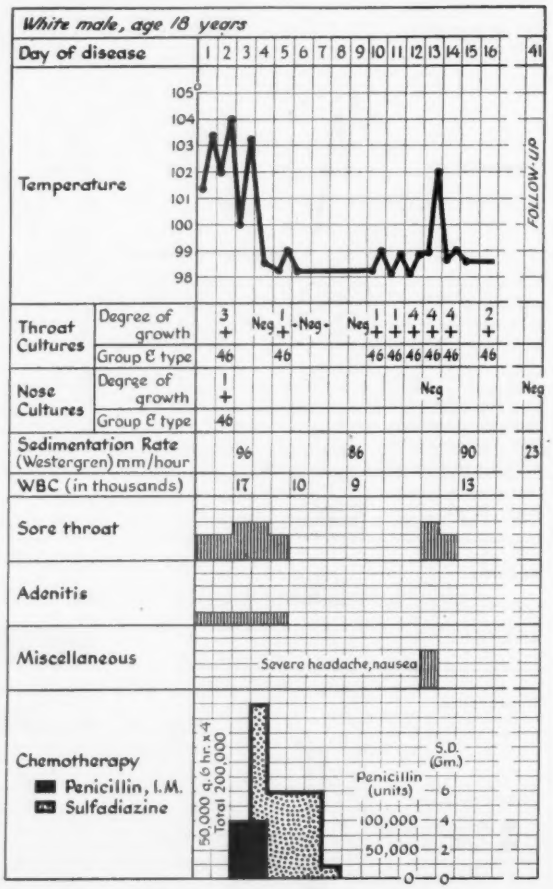

Chart 11.—Effect of 200,000 units of penicillin followed by 27 Gm. of sulfadiazine on the clinical course of severe tonsillitis. Note the clinical and bacteriologic relapse.

In summary, essentially the same clinical response was obtained in patients with tonsillitis when a relatively small total dose of penicillin was followed by therapy with sulfadiazine as was previously described for penicillin. It is significant that a majority of the patients had negative cultures of material from the nose and throat while therapy

was being given. This was primarily due to the penicillin and not to the sulfadiazine. Shortly after therapy with sulfadiazine had been discontinued, the majority of patients had bacteriologic relapses, and in some instances there was a clinical relapse. The mechanism of these relapses has been previously discussed and is possibly related to therapy with penicillin. On the basis of these observations, it would appear that there is no advantage in the use of sulfadiazine in conjunction with penicillin except for patients with unusually severe tonsillitis and patients with complications.

Treatment of Scarlet Fever with Penicillin or Penicillin and Sulfadiazine.—An attempt was made to evaluate penicillin or penicillin and sulfadiazine for patients with scarlet fever. During the period of this investigation the number of cases encountered was relatively small, and, since only the more severely ill patients were selected for the treatment, only 15 were studied. The doses of penicillin and sulfadiazine which were administered and other clinical and bacteriologic data are given in table 8.

Only 2 patients received penicillin alone. One patient received 300,000 units, and a second was given 1,000,000 units. Fairly satisfactory clinical results were obtained in both instances. While the improvement was not dramatic, definite benefit was noted within the first twenty-four hours of therapy. The following case demonstrates the effect of relatively small doses of penicillin on scarlet fever:

CASE 1.—An 18 year old white youth entered the station hospital on Feb. 14, 1944. The day before entry he had a sudden onset of sore throat and fever. On the third day in the hospital, or the fourth day of his illness, he appeared extremely toxic. He had a mild erythematous eruption on his trunk. There was a hemorrhagic rash on the soft palate. The tonsils and pharynx were extremely inflamed, with exudate covering the tonsillar surfaces. A severe bilateral cervical adenitis was present. Type 30 streptococci were obtained from cultures of material from the nose and throat. On the third day of his illness the patient was given 25,000 units of penicillin intramuscularly every four hours for twelve doses, or a total of 300,000 units. On the second day of treatment he felt much better. The rash was less, the redness of the pharynx had diminished, only a slight amount of exudate was present on the tonsils and the adenitis had almost subsided. He continued to improve steadily. The rash was completely absent forty-eight hours after therapy. He made an uneventful recovery. Hemolytic streptococci were not eradicated from the throat. The clinical course of this patient is illustrated in chart 12.

The remaining 13 patients were given penicillin in total doses varying between 200,000 and 400,000 units followed by therapy with sulfadiazine. In general, fairly satisfactory clinical results were obtained. Chart 13 shows a composite chart with the effect of combined therapy on the temperatures of 9 patients with scarlet fever. All the patients improved coincident with therapy. The effect with

TABLE 8.—*Effect of Penicillin Administered Intramuscularly or Penicillin and Sulfadiazine on the Clinical Course and Bacteriologic Status of Patients Having Scarlet Fever*

Total Dose of Penicillin in Units, and Method of Administration	Total Dose Sulfadiazine	Interval Between Initial Treatment and Normal Temperature	Bacteriologic Observations; Group and Type of Hemolytic Streptococci and Quantitative Culture				Comments
			Before Treatment		After Treatment		
			Nose	Throat	Nose	Throat	
300,000—25,000 every 4 hr. × 12....	.....	96 hr.	Type 30, 1+	Type 30, 4+	Type 30, 4+	Type 30, 4+	Fair response
1,000,000—50,000 every 4 hr. × 20...	.....	48 hr.	Type 3, 4+	Type 3, 2+	Negative	Type 19, 1+	Fair response; reinfection without symptoms
200,000—50,000 every 4 hr. × 4.....	18 Gm. 4 days	96 hr.	Type 30, 2+	Type 30, 3+	Type 30, 4+	Type 30, 4+	Fair response
200,000—50,000 every 4 hr. × 4.....	28 Gm. 5 days	5 days	Negative	Type 19, 3+	Negative	Type 19, 3+	Fair response; on day following conclusion of therapy temperature 100 F. and lasting 6 days
200,000—50,000 every 4 hr × 4.....	37 Gm. 6 days	72 hr.	Type 19, 4+	Type 19, 4+	Type 19, 1+	Type 19, 2+	Questionable effect
200,000—50,000 every 4 hr. × 4.....	26 Gm. 5 days	5 days	Negative	Type 30, 1+	Negative	Negative	Fair response
200,000—50,000 every 4 hr. × 4.....	24 Gm. 4 days	96 hr.	Type 17, 2+	Type 17, 1+	Group C, 2+	Group C, 3+	Fair response; 3 days after conclusion of therapy temperature 99 F., with tonsillitis and adenitis on 6th day
200,000—25,000 every 4 hr. × 8.....	25 Gm. 5 days	72 hr.	Type 17, 1+	Type 17, 4+	Negative	Type 17, 1+	Fair response
200,000—25,000 every 4 hr. × 8.....	30 Gm. 5 days	72 hr.	Type 3, 4+	Type 3, 4+	Negative	Type 1, 1+	Fair response; readmitted 1 week after discharge, 22 days after therapy, with acute rheumatic fever and type 1 organisms in throat
200,000—25,000 every 4 hr. × 8.....	26 Gm. 5 days	48 hr.	Type 17, 4+	Type 17, 1+	Negative	Type 0,* 3+	Reinfection; slight febrile relapse on 4th and 5th days after therapy
200,000—50,000 every 6 hr. × 4.....	33 Gm. 6 days	96 hr.	Type 19, 4+	Type 19, 4+	Type 19, 1+	Type 19, 3+	Fair response; 5 days after therapy temperature 99 F., with aches and pains lasting 8 days
200,000—50,000 every 6 hr. × 4.....	33 Gm. 6 days	96 hr.	Type 19, 4+	Type 19, 3+	Type 19, 4+	Type 19, 4+	Readmitted 19 days after treatment, with acute rheumatic fever; type 19 organisms still in nose and throat
200,000—50,000 every 6 hr. × 4.....	27 Gm. 5 days	6 days	Type 19, 2+	Type 19, 4+	Type 19, 2+	Type 19, 3+	Fair response; 6th day after treatment slight fever and sore throat
350,000—50,000 every 4 hr. × 7.....	50 Gm.	5 days	Type 3, 4+	Type 3, 3+	Negative	Type 3, 1+	Fair response; mastoiditis aborted
400,000—25,000 every 4 hr. × 16....	14 Gm. 3 days	96 hr.	Type 17, 4+	.....	Negative	Type 17, 3+	Fair response; urticaria due to penicillin or sulfadiazine

* Type 0 = unable to type.

penicillin appeared to be more promising than that experienced with sulfadiazine but not so beneficial as that obtained with the use of specific antitoxin. Though antitoxin was not evaluated in this investigation, previous experience had demonstrated prompt improvement in patients with severe scarlet fever who had received antitoxin. Poststreptococcic fever was observed in several patients after the cessation of therapy, and clinical relapses with sore throat and fever were

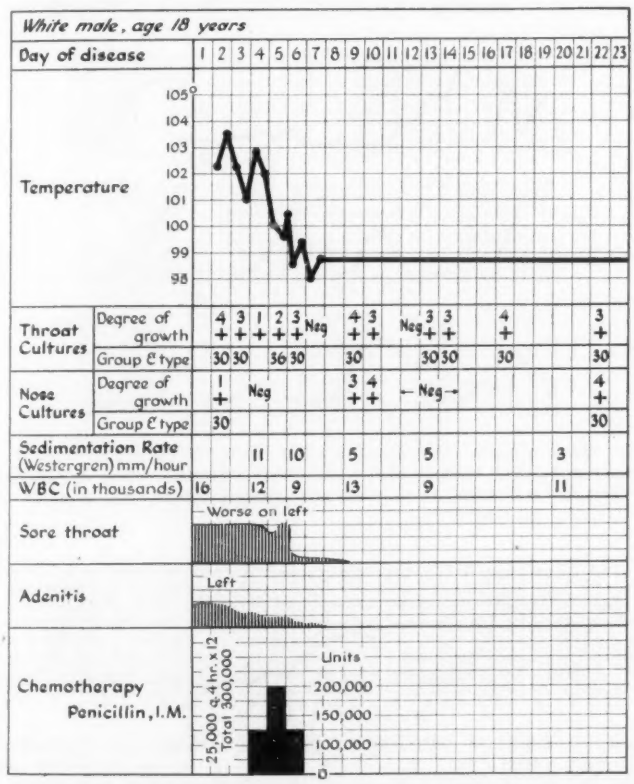

Chart 12.—Effect of 300,000 units of penicillin on the clinical course of scarlet fever. Note that hemolytic streptococci reappeared in the nose and throat before discharge from the hospital.

associated with the reappearance of streptococci in cultures of material from the throat. Acute rheumatic fever developed in 2 patients (patients 9 and 12). One patient had urticaria due to either the penicillin or the sulfadiazine. Chart 14 presents composite data for patients with scarlet fever and the response to different types of therapy.

The failure to obtain a prompt response with penicillin and sulfadiazine in a patient with scarlet fever is demonstrated by the following case.

A 32 year old white man entered the station hospital on March 18, 1944. The day before entry sore throat, headache and vomiting developed. On entry he appeared decidedly toxic. The day after entry, or on the third day of his illness, he had the typical erythematous eruption of scarlet fever on his trunk and extremities. There were extreme redness and edema of the uvula and pharynx. Though his tonsils were absent, there was exudate on the uvula and in the tonsillar fossae.

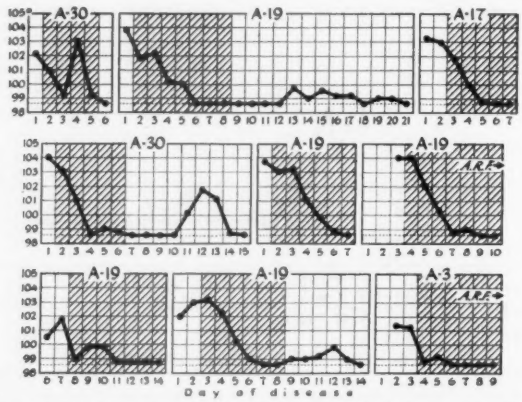

Chart 13.—Composite chart showing effect of 200,000 units and sulfadiazine on the temperatures of 9 patients with scarlet fever. Hatched areas indicate periods when penicillin and sulfadiazine were administered. Note that acute rheumatic fever developed in 2 patients.

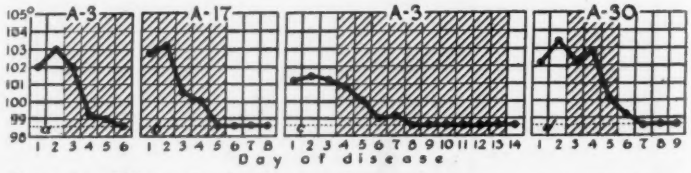

Chart 14.—Effect of miscellaneous forms of treatment on temperatures of patients with scarlet fever: *a*, 1,000,000 units of penicillin; *b*, 400,000 units of penicillin followed by sulfadiazine; *c*, 350,000 units of penicillin, followed by sulfadiazine, and *d*, 300,000 units of penicillin.

Slight bilateral cervical adenitis was present. Type 19 streptococci were isolated from the nose and throat on culture. He was given a total of 200,000 units of penicillin in four doses of 50,000 units every six hours. With the last dose of penicillin, sulfadiazine was administered for a total dose of 33 Gm. in six days. A concentration of 6.5 mg. of free sulfadiazine in the blood was obtained. On the second day of therapy he was improved, though still ill and unable to eat. There was less edema of the pharynx. On the third day he was improved and eating a little. The rash was subsiding, and only a slight amount of exudate was

present on the uvula. On the fourth day the pharynx appeared normal and his appetite was fair. On the fifth day he still had a slight sore throat but the rash had disappeared. There was desquamation of the skin on the seventh day. After therapy the same type of streptococci were cultured from his throat. He also had late poststreptococcic fever. The clinical course of this patient is illustrated in chart 15.

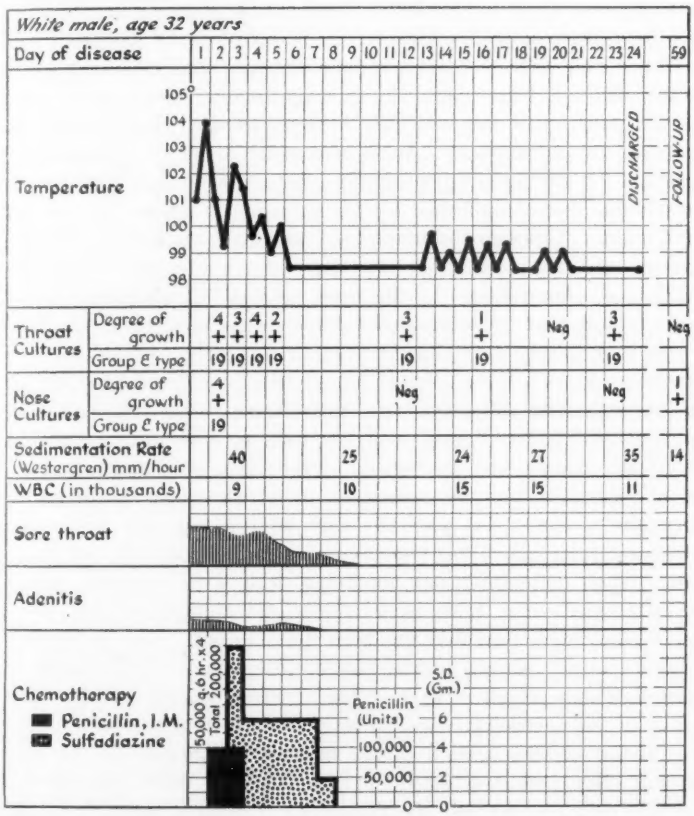

Chart 15.—Effect of 200,000 units of penicillin followed by 33 Gm. of sulfadiazine on scarlet fever. Note the failure to eradicate hemolytic streptococci from the pharynx and also the poststreptococcic fever.

In summary, it would appear that penicillin and, particularly, penicillin and sulfadiazine are limited in their value against scarlet fever. Specific antitoxin should be given to patients having severe scarlet fever. Penicillin, and possibly sulfadiazine, should be reserved for the suppurative lesions which follow invasion of the tissues by the bacterial cell. This includes instances of severe tonsillitis or pharyngitis with cervical

adenitis, early peritonsillar abscesses and otitis media. In many cases scarlet fever is a relatively mild infection and specific therapy is not necessary.

COMMENT

It must be emphasized that the investigations being reported on were concerned with young men who were in good health prior to the sudden onset of a hemolytic streptococcus infection of the upper respiratory tract or scarlet fever. The majority of the patients treated would probably have recovered without serious complications if specific therapy had not been used. In this age group, streptococcic tonsillitis and pharyngitis run relatively benign courses. Suppurative complications are uncommon. Acute rheumatic fever is apparently not prevented by the administration of sulfadiazine or penicillin once an infection has been established by the invasion of tissues by hemolytic streptococci. Although the number of patients treated was small, sulfadiazine did not appear to shorten the clinical course of either tonsillitis or pharyngitis. In the more severely ill patients there was some evidence that sulfadiazine did diminish the severity of the disease so that they were more comfortable at an earlier period than the untreated controls. The clinical effect with penicillin was more pronounced than that obtained with sulfadiazine. The severity of the symptoms was reduced more promptly, and, in some instances at least, the clinical course was shortened. There are two disadvantages in use of penicillin for the treatment of streptococcic tonsillitis and pharyngitis. First, the material must be injected into the patients at frequent intervals. This is a decided inconvenience in most circumstances when these infections are being dealt with. Second, patients not infrequently may have bacteriologic and clinical relapses shortly after therapy with penicillin has been discontinued. The pathogenesis of these clinical relapses merits further discussion. The concept was entertained that penicillin, as a potent antistreptococcic agent, inhibited growth of the micro-organisms to such a degree that the bacterial cells were absent on the surface of the mucous membranes of the throat but that they persisted deeper in the tissues. When therapy with penicillin was discontinued, the remaining organisms began to multiply and found their way to the surface again. There existed the possibility that by a reduction of the numbers of streptococci with penicillin, but not an entire elimination of them, the immunologic mechanism was disturbed in an unfavorable manner for the host. The natural course of tonsillitis and pharyngitis, and particularly recovery from the diseases, may depend on the presence of streptococci in the throat in sufficient numbers to serve as antigenic material, thus producing local tissue immunity or, possibly, a general immune response. Reducing the numbers of streptococci or altering their metabolic activity with

penicillin might possibly interfere with a desired immune mechanism. With the failure of the host to develop this immunity or because of a partial immunity, the multiplying bacterial cells at the conclusion of therapy with penicillin cause a recurrence of the disease and, in addition, complications. Sulfadiazine, on the other hand, does not interfere with bacterial activity to such an extent that the drug interferes with the immune mechanism. Therefore, relapses do not occur so frequently following the use of sulfadiazine. Obviously, the ideal therapy would be to eliminate streptococci completely from the tissues early in the course of the disease, but the doses of penicillin did not produce this desired result.

Therapy with sulfadiazine did not appear to eradicate streptococci from the pharynx of patients with tonsillitis, pharyngitis and scarlet fever to any greater degree than that manifested in untreated control patients. On the other hand, when as little as 200,000 units of penicillin was given in divided doses, hemolytic streptococci were often absent from the nose and throat during the period of therapy. More than temporary eradication of streptococci from the pharynx was accomplished only with total doses of 500,000 to 1,000,000 units. It appeared that the time over which penicillin is given is as important as the total dose used in the attempt to eradicate streptococci from the throat. This fact is significant in any efforts that are made to eliminate the carrier state of hemolytic streptococci.

Since sulfadiazine did not appear to shorten the clinical course of patients with tonsillitis or pharyngitis and did not eliminate streptococci from their throats, use of sulfadiazine in these infections is definitely indicated only for persons with severe forms of these diseases and for those with suppurative complications. In general, this also applies to penicillin. Total doses of 200,000 units of penicillin may be anticipated to produce some relief for the patients, but doses of 500,000 to 1,000,000 units are necessary if it is desired to eliminate streptococci from the pharynx. There does not appear to be any advantage, at least for the majority of patients, in following up penicillin with sulfadiazine.

Specific antitoxin or serum from patients convalescing from scarlet fever is to be preferred to sulfadiazine and penicillin in the treatment of patients with severe scarlet fever. Sulfadiazine, and especially penicillin, are indicated for the local inflammatory reaction in the throat and suppurative complications.

It is significant that sulfadiazine or penicillin in the doses used did not prevent the development of acute rheumatic fever in patients with infections of the upper respiratory tract due to group A hemolytic streptococci.

SUMMARY

1. An investigation of the therapeutic effectiveness of sulfadiazine and penicillin for acute infections of the upper respiratory tract due to hemolytic streptococci, including scarlet fever, involved observations carried out in a total of 210 young men in one area during a period of four months.

2. Cultures of materials from the nose and throat were made, and when hemolytic streptococci were isolated grouping and typing of the organisms were performed according to the method of Lancefield. Approximately 2,000 cultures were studied during the course of this investigation.

3. One hundred and two patients having acute tonsillitis or nasopharyngitis were used as a control series and did not receive sulfadiazine or penicillin. Seventeen patients with tonsillitis or nasopharyngitis were given sulfadiazine. Thirty patients with moderate to severe forms of tonsillitis and 9 patients having severe nasopharyngitis received penicillin. Penicillin was also given to 8 patients with nonstreptococcic infections of the upper respiratory tract, 2 patients with scarlet fever and 1 with erysipelas. Penicillin followed by sulfadiazine was administered to 13 patients with scarlet fever and to 16 patients with tonsillitis.

4. Sulfadiazine did not shorten the clinical course of patients with tonsillitis or eradicate hemolytic streptococci from the pharynx. In severely ill patients the drug did appear to diminish the severity of the disease more rapidly than the natural diminution which occurred in the untreated controls.

5. Total doses of 200,000 units of penicillin given intramuscularly to patients with severe tonsillitis and nasopharyngitis reduced the severity and in some instances appeared to shorten the duration of the disease. Doses of 500,000 to 1,000,000 units were necessary before hemolytic streptococci were eliminated from cultures of material from the throat for more than a temporary period.

6. Clinical relapses following the administration of penicillin were frequently encountered and appeared to be related to the reappearance of hemolytic streptococci in the throat.

7. Penicillin followed by sulfadiazine did not appear to have any advantages over penicillin alone in the treatment of tonsillitis. This combination did not produce too satisfactory results in patients having scarlet fever.

8. Penicillin did not appear to prevent the subsequent development of acute rheumatic fever in patients having nasopharyngitis, tonsillitis and scarlet fever due to group A hemolytic streptococci.

REITER'S DISEASE

Review of the Literature, with Presentation of a Case

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THE triad of symptoms consisting of urethritis, conjunctivitis and arthritis, common in gonorrhea, has more recently been observed in patients in whom the etiologic role of the gonococcus could not be established. The first case was described by Reiter [1] in Germany in 1916. During the first world war this German physician observed a lieutenant on the eastern front who was suffering from abdominal cramps and bloody diarrhea. Later purulent urethritis and conjunctivitis appeared, followed shortly thereafter by arthritis of the left knee, right elbow, left wrist and joints of the fingers of the right hand, in that order. Subsequently cystitis, edema of the prepuce, iritis, enlarged spleen and pustular lesions over the left hip were noted. Reiter was unable to influence the disease by any of the therapeutic agents available to him. His major contribution is that he conceived of this syndrome as a new entity not ascribable either to dysentery or to gonorrhea. At about the same time two other clinicians made independent reports of this disease, Fiessinger [2] in France and Macfie [3] in Africa. Subsequently a large number of similar publications appeared in the French, German and Scandinavian literature.[4]

From the Second Medical Service of Dr. I. Snapper, the Mount Sinai Hospital, New York.

1. Reiter, H.: Ueber eine bisher unerkannte Spirochäteninfektion (Spirochaetosis arthritica), Deutsche med. Wchnschr. **42**:1535, 1916.

2. Fiessinger, N., and Leroy, E.: Contribution à l'étude d'une épidémie de dysenterie dans la Somme (Juillet-Octobre, 1916), Bull. et mém. Soc. méd. d. hôp. de Paris **40**:2030, 1916-1917.

3. Macfie, J. W. S.: Urethral Spirochaetosis, Parasitology **9**:274, 1917.

4. (*a*) Balban, W.: Zur Kenntnis der sog. "Spirochaetosis arthritica" (Reiter), Dermat. Ztschr. **68**:305, 1934. (*b*) Beck, F.: Ein Beitrag zu der sog. Spirochaetosis arthritica Reiter, Med. Klin. **33**:1162, 1937. (*c*) Besson, A., and Ehringer, G.: Diagnostic des arthrites dysentériques, Paris méd. **2**:328, 1926. (*d*) Gounelle, H.; Bohn, A.; Koskas, C., and Marche, J.: Sur la maladie rhumatismale post-dysentérique (formes fébriles prolongées, syndrome sanguin et humoral, altérations osseuses, essais thérapeutiques), Bull. et mém. Soc. méd. d. hôp. de Paris **56**:821, 1941. (*e*) Clemmesen, S., and Kalbeck, K.: Polyarthritis Urethrica Simplex in Four Patients, Ugesk. f. læger **100**:618, 1938. (*f*) Dorendorf: Der Ruhrrheumatism, Med. Klin. **13**:519, 1917. (*g*) Fleischmann, in discussion on Reiter.[1] (*h*)

(Footnote continued on next page)

The first American description appeared twenty-five years after the syndrome had been recognized in Europe. A report by Bauer and Engleman [5] describing the classic features of the disease in a young college student is apparently the first instance observed and recorded in the United States. It is also the only full report in the American literature, other contributions [6] being limited to special aspects of the disease.

Foerster, R.: Zwei Fälle von Reiterscher Erkrankung, Med. Welt **7**:700, 1933. (*i*) Freund, E.: Die Gelenkserkrankungen, Berlin, Urban & Schwarzenberg, 1928, p. 142. (*j*) Frühwald, R.: Beitrag zur sogenannten Spirochaetoses arthritica (Reiter), Dermat. Ztschr. **51**:35, 1927-1928. (*k*) Germain, A., and Pirot, R.: Syndrome conjonctivo-uréthro-synovial, complication métastatique d'un état dysentériforme, Arch. de méd. et pharm. nav. **125**:302, 1935. (*l*) Hombourger, P.: Syndromes oculo-articulaire d'origine dysentérique, Soc. de méd. mil. franç., Bull. mens. **22**:33, 1928; (*m*) Contribution à l'étude des complications oculaires, et articulaires de la dysentérie bacillaire (syndrome conjunctivo, uretro, synovial de Noël Fiessinger), Rev. gén. de clin. et de thérap. **44**:459, 1930. (*n*) Junghanns, O.: Ein weiterer Fall von Urethritis nongonorrhoica und septischer Allgemeinerkrankung, Deutsche med. Wchnschr. **44**:1304, 1918. (*o*) Kielland, J.: Polyarthritis Dysenterica, Nord. med. **2**:984, 1939. (*p*) Kristensen, M.: Case Report on a Case of Reiter's Disease, Acta path. et microbiol. Scandinav. **7**:87, 1930. (*q*) Kristjansen, A.: Nongonorrheal Urethritis with Conjunctivitis and Arthritis, Ugesk. f. læger **92**:276, 1930. (*r*) Kruspe, H.: Zur Aetiologie der Reiterschen Erkrankung, Dermat. Wchnschr. **112**:457, 1941. (*s*) Kuske, H.: Ueber die Hauterscheinungen bei Morbus Reiter, Arch. f. Dermat. u. Syph. **179**:58, 1939. (*t*) Maresch and Chiari, H., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1931, vol. 6, p. 246. (*u*) Michael, M.: Beiträge zur Kasuistik und Differential-Diagnose seltener frühluetischer und gonorrhoischer Komplikationen, Dermat. Ztschr. **24**:406, 1917. (*v*) Musger, A.: Bakteriologische Untersuchungen an einen Fall mit Reiterschen Krankheit, Dermat. Ztschr. **68**:310, 1934. (*w*) Naegeli, cited by Kruspe.[4r] (*x*) Paetzel, H.: Ueber Polyarthritis nach unspezifischer Urethritis, Med. Klin. **24**:134, 1928. (*y*) Pfleger, R.: Zur Aetiologie der Reiterschen Erkrankung, ibid. **33**:465, 1937. (*z*) Postma, C.: A Case of Reiter's Disease, Acta dermat.-venereol. **18**:691, 1937. (*a'*) Reiter, H.: Ueber die Spirochaete forans, Zentralbl. f. Bakt. (Abt. 1) **79**:176, 1916-1917; (*b'*) Ueber die sogenannte "Spirochätosis arthritica" (Reiter), München. med. Wchnschr. **68**:950, 1921. (*c'*) Rist, S.: Arthropathies et conjonctivites dysentériques, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1762, 1916. (*d'*) Ruge, H.: Bemerkungen zu der Arbeit von Frühwald: "Spirochaetosis arthritica," Dermat. Ztschr. **54**:98, 1928. (*e'*) Salvesen, H. A.: Dysenteric Polyarthritis and Enteric Polyarthritis, Norsk mag. f. lægevidensk. **98**:953, 1937. (*f'*) Schittenhelm, A., and Schlecht, A.: Polyarthritis enterica, Deutsches Arch. f. klin. Med. **26**:329, 1918. (*g'*) Schittenhelm, A., in von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, ed. 3, Berlin, Julius Springer, 1934, vol. 1, p. 177. (*h'*) Scheuermann, H., cited by Kruspe.[4r] (*i'*) Sommer, A.: Drei wahrscheinlich als "Spirochaetosis arthritica" (Reiter) anzusprechende Krankheitsfälle, Deutsche med. Wchnschr. **44**:403, 1918. (*j'*) Stuehmer, A.: Ueber die sogenannte "Spirochaetosis arthritica" (Reiter), München. med. Wchnschr. **68**:769, 1921; (*k'*) Therapeutische Umfrage: Behandlungsaussichten der nichtspezifischen Urethritiden (Pseudogonor-

(Footnotes continued on next page)

The following case was recently observed at the Mount Sinai Hospital, New York.

REPORT OF CASE

History.—A 33 year old Jewish man entered the Mount Sinai Hospital on May 21, 1932 complaining of attacks of urethritis, conjunctivitis and arthritis accompanied by fever, which had recurred over an eight year period. The first attack was ushered in with a thick, mucoid discharge from the urethra. A number of days later fever developed associated with a migratory polyarthritis involving many joints, specifically the left knee, right ankle, spine and the shoulders. The affected joints were red, swollen and extremely tender for approximately one week. Concurrent with the arthritis an acute conjunctivitis developed with purulent discharge, which lasted for several weeks. He had had two such attacks, eight years and two years before admission. Both episodes lasted a few weeks, and all symptoms and findings disappeared completely. Aside from these episodes, two years before admission iritis of the left eye developed which responded to ordinary therapy. He entered the hospital in May 1932 because of recurrence of these symptoms.

Throughout the eight year period, during and following the attacks, many smears for gonococci, blood cultures and gonococcus complement fixation tests were negative.

Examination.—Physical examination revealed an undernourished man appearing chronically ill. The pupils were unequal and irregular, the left showing posterior synechiae, evidence of an old iritis. There was moderate conjunctivits of both eyes. The liver was palpable 1.5 cm. below the costal margin. The left wrist, left index and ring fingers, right ankle and left knee were tender, and their motion was slightly impaired. The thoracic vertebrae were markedly tender,

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rheum), Dermat. Wchnschr. **93**:1553, 1931. (*l'*) Thesleff, C.: Case of Non-Gonorrheal Urethritis with Articular and Ocular Complications, Finska läk.-sällsk. handl. **80**:411, 1937. (*m'*) Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1920, vol. 4, p. 394. (*n'*) Tiemann: Ueber die Polyarthritis rheumatica enterica, Ztschr. f. klin. Med. **122**:724, 1932. (*o'*) Wiedemann, H.: Reitersche Erkrankung, Wien. klin. Wchnschr. **47**:1245, 1934. (*p'*) Worms, G.; Lesbre, P., and Sourdille, G.: Specificité des infections oculo-articulaires tardives dans les dysentéries bacillaires, Compt. rend. Soc. de biol. **95**:1042, 1926. (*q'*) Worms, G., and Sourdille, G.: Complications oculaires des entéropathies à germes spécifiques, Arch. d'opht. **45**:737, 1928. (*r'*) Worms, G.; Sourdille, G., and Lesbre, P.: Syndrome oculo-articulaire au décours d'une épidémie de dysentérie à bacilles de Hiss, Bull. Soc. d'opht. de Paris, 1927, pp. 21-28. (*s'*) Worms, G.; Lesbre, P., and Sourdille, G.: Syndrome oculo-articulaire au décours d'une épidémie de dysénterie à bacilles de Hiss, Soc. de méd. mil. franç., Bull. mens. **21-22**:29, 1927-1928.

5. Bauer, W., and Engleman, E. P.: A Syndrome of Unknown Etiology Characterized by Urethritis, Conjunctivitis and Arthritis (So-Called Reiter's Disease), Tr. A. Am. Physicians **57**:307, 1942.

6. (*a*) Colby, F. H.: Renal Complications of Reiter's Disease, J. Urol. **52**:415, 1944. (*b*) Lever, W. F., and Crawford, G. M.: Keratosis Blennorrhagica Without Gonorrhea (Reiter's Disease?), Arch. Dermat. & Syph. **49**:389 (June) 1944. (*c*) Rosenblum, H. H.: So-Called Reiter's Disease: The Triad of Acute Arthritis, Conjunctivitis and Urethritis, U. S. Nav. M. Bull. **44**:375, 1945.

particularly the third and seventh. The urethral meatus was reddened. The prostate was normal; the skin was clear. Neurologic examination revealed no abnormalities.

Laboratory data.—Blood culture was negative and prostatic fluid obtained by massage contained no gonococci. Reactions to the Wassermann and gonococcus complement fixation tests were repeatedly negative. The urine was normal. Fluid aspirated from the left knee joint was cultured one week before admission and was reported negative. The electrocardiogram was normal. Roentgen examination of the left knee showed irregular areas of rarefaction of the condyles, a finding which was interpreted as a destructive process.

Course.—During his two months in the hospital the temperature ranged between 99 and 101 F., finally falling to normal. Under observation bilateral herpetic corneal ulcers developed, which responded to administration of atropine and use of hot compresses. To eliminate possible foci of infection, tonsillectomy was performed. This was followed by transient arthralgias.

The patient was finally discharged to his private physician with recommendations for physical therapy.

Second Admission.—On Feb. 11, 1935, the patient was again admitted to the hospital. He had remained well and asymptomatic. He had carried on his occupation and participated in vigorous sports without disability until seven weeks before admission, when general malaise and vague aches and pains in the back and arms gradually developed. This was soon followed by a heavy urethral discharge lasting two weeks. Urethral smears again failed to reveal gonococci. A week after the onset of the discharge in rapid succession there developed pain, swelling and tenderness of both hip joints, right knee, both ankles, right elbow and left wrist, lasting about one week. At the same time a painful bilateral conjunctivitis appeared, worse in the right than in the left eye. He had a low grade fever, with a temperature up to 100 F. During the early part of the illness he suffered from severe anorexia and nausea; he vomited frequently, slept poorly and lost 20 to 30 pounds (9 to 13 Kg.) during this period. A week after the onset of the illness, a herpetiform lesion appeared on the glans penis, which ruptured and gradually healed. The scar was present on admission. There were no other cutaneous manifestations.

On physical examination the right eye showed circumcorneal injection and numerous superficial infiltrations at 5 and 7 o'clock near the limbus. No deposits were seen on the posterior surface of the cornea. This was considered to be a mild, superficial herpetic keratitis. The left eye showed multiple posterior synechiae. There were several erythematous, glazed areas with brownish crusts on the glans penis. The urethral meatus was normal and contained no discharge even after prostatic massage. Rectal examination gave normal results. The right elbow was slightly tender and warm, with moderate periarticular swelling and definite limitation of extension. The left wrist was tender, stiff and somewhat swollen, with marked swelling of the third left metacarpophalangeal joint. There was a small effusion in both knee joints, and both ankles were tender.

Laboratory Data: Hemoglobin was 70 per cent (Sahli). The white cell count was 14,400 with a normal differential count. The erythrocyte sedimentation time was ten minutes (Linzenmeier). The urine was normal. The Wassermann and gonococcus complement fixation reactions were again negative. Blood culture was negative. Cultures of the prostatic secretions were negative for the gonococcus.

Course: The temperature ranged between 99.5 and 100.6 F. for the first two weeks. Iritis and keratitis soon developed in the left eye, but gradually cleared. A tonsillar stump was surgically removed. Following operation there was a flare-

up of fever, conjunctivitis, iritis and arthritis but not of the urethritis. The symptoms and signs gradually subsided with symptomatic therapy.

Third Admission.—The patient was admitted on June 25, 1941 for a recurrence of severe polyarthritis and urethritis and herpes of the penis. During this episode there were no ocular manifestations or fever. The patient had lost 30 pounds in the three months prior to admission.

Physical examinations on this admission gave essentially the same results as on preceding occasions except for the following additions: The right pupil was fixed to light; there was a lenticular cataract limiting vision to light perception. The liver was palpable 2 cm. below the costal margin. There was a flexion contracture of the right elbow. The left ankle was slightly swollen and there was tenderness over the tenth and eleventh thoracic vertebrae and the first metacarpophalangeal joints.

Laboratory examination revealed the following significant findings: Culture of the urine showed enterococci. The erythrocyte sedimentation time was fifteen minutes. The hemoglobin was 65 per cent. The electrocardiogram, which had previously been normal, now revealed a P-R interval of 0.26 second and slight elevation of the R-T segments in leads II and III. Roentgen examination of the left hip showed no abnormality, but in the dorsal part of the spine there were calcified deposits in the lateral spinous ligaments. The patient was given 400 r of roentgen radiation to the dorsal part of the spine. He was discharged somewhat improved.

Fourth Admission.—The patient was again admitted on March 17, 1943. Five days before admission a watery, urethral discharge developed associated with mild dysuria and followed four days later by a moderate polyarthritis. The right eye was atrophic. There was an iris bombé in the right eye and a streak of exudate at the pupillary margin of the left eye. The pharynx was injected. The lungs were clear. The blood pressure was 110 systolic and 70 diastolic. There was no glandular adenopathy. The abdomen was normal. The urethral meatus was reddened, the prostate large and boggy. The dorsal spine was painful and tender. Redness and heat were present over the dorsum of the right foot and over the upper third of the left fibula.

On laboratory examination the blood count and urinalysis gave normal results. The urethral smear did not contain gonococci, nor were they found in cultures of the prostatic secretions. All serologic reactions, including a brucella agglutination, were negative as before. Blood urea nitrogen was 10 mg. per hundred cubic centimeters, sugar 85 mg., total protein 7 Gm., albumin 4.6 Gm., globulin 2.4 Gm. and uric acid 4.6 mg. Fluid from the knee joint was sterile on culture. The electrocardiogram revealed a P-R interval of 0.2 second and prominent P waves. Roentgen examination of the lungs and hands showed that they were normal. Slight osteoarthritic changes were present in the left knee joint. Calcification was present in the lateral spinous ligaments in the lower thoracic region.

No other foci of infection could be found. The patient was treated with hyperthermia, both by typhoid vaccine and by external heat, but was not benefited. Toward the end of his stay in the hospital he became uncooperative. He refused therapy and was discharged for chronic care.

COMMENT

The earliest sign of this syndrome is frequently diarrhea. If this is absent the disease may begin with either urethritis or conjunctivitis.

The cases published in the French literature were always preceded by diarrhea, and apparently these clinicians were unwilling to diagnose the disease unless it followed an episode of diarrhea. Most of the German writers, on the other hand, recognized that although the majority of these patients do have diarrhea as an initial sign, approximately one third of the cases began with either conjunctivitis or urethritis and never presented an enteric episode.[4x]

When the diarrhea does occur it is usually mild.[7] A low grade fever is commonly present, but by and large the enteric symptomatology is so light that only specific questioning brings out the history. Bloody stools have been noted occasionally.

The enteric phase of the disease usually subsides in less than a week [8] and the patient remains well until ten to thirty days later, when a purulent conjunctivitis and urethritis appear. The conjunctivae become hyperemic and edematous and a yellowish mucopurulent discharge appears.[4q'] Most commonly only conjunctivitis results but occasionally keratitis,[9] iritis and iridocyclitis [10] occur, as they did in the patient whose case I have reported. Urethritis appears at about the same time, preceding or following the conjunctivitis by one or two days. The patient complains of dysuria and frequency.[1] A yellow, mucopurulent discharge exudes freely from the urethra. Not infrequently cystitis,[11] prostatitis [5] and prostatic abscess [6a] have been noted. Colby [6a] describes pyelonephritis as a complication of the syndrome. The urethritis and conjunctivitis persist throughout the entire course of the disease, with occasional remissions and exacerbations.

As the disease progresses, the weight-bearing joints, particularly those of the ankle and knee, become acutely inflamed and tender.[12] Less commonly the hips, shoulder, wrists, finger joints or even the vertebral column are affected.[13] Usually multiple joints are involved, and the arthritis is migratory, resembling the picture of acute rheumatic arthritis. Tendovaginitis has been described.[14] The roentgen examination does not reveal destructive changes, and usually full function remains. However, ankylosis has been reported [15] and was found to

7. Hombourger.[4m] Schittenhelm and Schlecht.[4f']

8. Reiter.[1] Hombourger (footnote 4*l* and *m*). Schittenhelm and Schlecht..[4f'] Worms, Lesbre and Sourdille.[4p'] Worms and Sourdille.[4q'] Worms, Sourdille and Lesbre.[4r'] Worms, Lesbre and Sourdille.[4s']

9. Beck.[4b] Worms and Sourdille.[4q']

10. Reiter.[1] Freund.[4l] Worms and Sourdille.[4q']

11. Reiter.[1] Sommer.[4l'] Bauer and Engleman.[5] Colby.[6a]

12. Schittenhelm and Schlecht.[4f'] Hombourger.[4m] Kuske.[4s]

13. Reiter.[1] Schittenhelm and Schlecht.[4f'] Hombourger.[4m]

14. Dorendorf.[4f] Schittenhelm and Schlecht.[4f']

15. Paetzel.[4x] Lever and Crawford.[6b]

be present in my case. Hydroarthroses are common and usually resolve spontaneously.[16] Serous fluid with low protein content is obtained on tap. Lymphocytes and polymorphonuclear cells are present in about equal proportion. Culture of the joint fluid is sterile.

During this period the patient has a low grade fever.[17] There is usually no anemia, but a moderate elevation of the polymorphonuclear cell count has been described by almost all observers, as well as an increase in the erythrocyte sedimentation rate.

Physical examination frequently reveals generalized lymphadenopathy especially of the axillary and inguinal nodes.[18] Occasionally a moderate splenomegaly is found.[19] Pleuritis has been mentioned.[4f] In a minority of cases and late in the disease lesions of the skin appear.[20] These begin as small superficial vesicles, change into shallow ulcers and finally heal, leaving hyperkeratotic scars. This complication has been described independently of Reiter's disease as keratosis blenorrhagica of nongonorrheal etiology.[21] The site of predilection is usually over the affected joints, especially in the lower extremities, and over the scrotum and penis. In the latter areas the lesions of the skin resemble herpes progenitalis in their early stages.

In 2 cases epistaxis was a frequent event [22] and in 1 an abnormally prolonged clotting time and poor clot retraction were found.[4d] In 1 other case bilateral involvement of the pyramidal tract was noted.[18b] Because of the infrequency of these manifestations they must be regarded as incidental.

Incomplete syndromes have occurred. Urethritis and arthritis without either conjunctivitis or cutaneous lesions have been observed.[23]

16. (*a*) Wepler, W.: Zur Morphologie und Pathogenese der post-dysenterischen Polyarthritis, Beitr. z. path. Anat. u. z. allg. Path. **106**:289, 1942. (*b*) Hombourger.[4m] (*c*) Worms, Lesbre and Sourdille.[4p] (*d*) Schittenhelm and Schlecht.[4f] (*e*) Bauer and Engleman.[5]

17. Reiter.[1] Hombourger.[4m] Schittenhelm and Schlecht.[4f] Worms and Sourdille.[4q]

18. (*a*) Moltke, O.: Polyarthritis Urethritica, Acta med. Scandinav. **89**:606, 1936. (*b*) Usseglio, G., and Zancan, B.: Il morbo di Reiter, Arch. per le sc. med. **69**:79, 1940. (*c*) Postma.[4g] (*d*) Bauer and Engleman.[5]

19. Reiter.[1] Usseglio and Zancan.[18b]

20. (*a*) Baermann, G.: Ueber hyperkeratotische Exantheme bei schweren gonorrhoischen Infektionen, Arch. f. Dermat. u. Syph. **69**:363, 1904. (*b*) Beck.[4b] (*c*) Kuske.[4s] (*d*) Postma.[4g] (*e*) Bauer and Engleman.[5] (*f*) Lever and Crawford.[6b]

21. Buschke, A., and Michael, M. J.: Zur Kenntnis der hyperkeratotischvesikulösen Exantheme bei Gonorrhoe, Arch. f. Dermat. u. Syph. **120**:348, 1914. Chajes, B.: Ueber nichtgonorrhoische Urethritiden und ihre Komplikationen, Dermat. Centralbl. **17**:194, 1913-1914.

22. Gounelle, Bohn, Koskas and Marche.[4d] Hombourger.[4m]

23. Kristjansen.[4q] Bauer and Engleman.[5] Moltke.[18a] Baermann.[20a]

Conjunctivitis and diarrhea both with and without arthritis have also been noted.[24]

It is necessary to differentiate Reiter's disease from the gonorrheal syndrome consisting of urethritis, conjunctivitis and arthritis. This differentiation can be made only by thorough bacteriologic investigation. In Reiter's disease bacteriologic studies of blood, urethral and conjunctival secretions and joint fluid never reveal gonococci. The reaction to the gonococcus complement fixation test is always negative.

AGE AND SEX

Reiter's disease probably occurs only in men. Most cases have been in men in their early twenties, the youngest patient whose case was reported being 16[4n] and the oldest 45. Only 1 case in a female has been described,[6b] and this was so atypical in other respects as to cast doubt on its being a case of Reiter's disease.

GEOGRAPHIC DISTRIBUTION

Although most of the observed instances of this disease have been in Germany, France and Scandinavia, it is probable that this distribution merely reflects the earlier interest of European physicians. Similar cases were described by Woodward[25] in his "Medical and Surgical History of the War of the Rebellion." More recently 10 cases have been reported in American soldiers on duty in the Pacific area[6c] and Bauer and Engleman[5] report that they have seen 6 cases in Boston.

It might be assumed from the infrequent mention of this disease in the literature that it is of rare occurrence. However, certain clinicians, notably Fiessinger,[2] Hombourger,[4l,m] Worms and Sourdille,[26] and Schittenhelm and Schlecht[4f'] have each observed a considerable number of cases, Hombourger reporting 56. It seems likely therefore that many cases in which the condition is being regarded now as nonspecific

24. (*a*) Graham, G.: Arthritis in Dysentery: Its Causation, Prognosis and Treatment, Proc. Roy. Soc. Med. **13**:23, 1919. (*b*) Graham, D., in Nelson's Loose-Leaf Medicine, New York, Thos. Nelson & Sons, 1937, vol. 2, p. 172. (*c*) Maxwell, E. M., and Kiep, W. H.: Notes on Six Cases of Iritis and Cyclitis Occurring in Dysenteric Patients, Brit. J. Ophth., **2**:71, 1918. (*d*) Pemberton, R.: The Relation of the Gastrointestinal Tract to the Syndrome of Arthritis, Rev. Gastroenterol. **9**:91, 1942. (*e*) Pribram, A.: Der akute Gelenksrheumatismus, Vienna, A. Holder, 1899, pp. 397-399. (*f*) Pillat, A.: Augenärztliches zum Rheumatismusproblem, Wien. klin. Wchnschr. **49**:385, 1936. (*g*) Zia, S. H., and Smyly, H. J.: Arthritis in Association with Bacillary Dysentery, Nat. M. J. China **17**:307, 1931. (*h*) Schittenhelm and Schlecht.[4f'] (*i*) Schittenhelm.[4g']

25. Woodward, J. J.: Medical and Surgical History of the War of the Rebellion, Washington, D. C., Government Printing Office, 1879

26. Worms, Lesbre and Sourdille.[4p'] Worms and Sourdille.[4q'] Worms, Sourdille and Lesbre[4r'] Worms, Lesbre and Sourdille.[4s']

conjunctivitis and urethritis or as rheumatoid arthritis may well be examples of Reiter's disease.

PATHOLOGY

In only 2 cases were the pathologic tissues from patients with this disease examined. Bauer and Engleman [5] studied a small piece of synovial tissue removed for biopsy from the left knee joint, and found a suggestion of villous formation in the suprapatellar pouch. On microscopic examination the intima was found to be several cells deep, and contained a moderate excess of lymphocytes and plasma cells and a few leukocytes. There was no evidence of exudate, and no inclusion bodies were found. A scant, diffuse infiltration of inflammatory cells was present throughout the subintimal layers. The pathologic diagnosis was mild synovitis with marked hyperemia.

Almost the same microscopic changes were reported by Wepler,[16a] who observed a case of typical Reiter's disease following an intestinal disorder. The patient apparently died of massive bleeding in the gastrointestinal tract. At postmortem examination a rupture of a submucous vessel in the wall of the stomach was found. There was no ulcer, no thrombus and no inflammatory response. Examination of the knee showed normal cartilage with a greenish yellow fluid in the joint. Microscopically there were edema of the synovia and disappearance of the synovial lining cells. The joint capsule was infiltrated with lymphocytes, as was the periarticular tissue. The joint exudate consisted mainly of polymorphonuclear cells. Cartilage and bone showed no changes from the normal.

FREQUENCY AND PROGNOSIS

A total of 151 cases have been reported in the literature to date. As indicated in the foregoing text, most of them were seen in Germany and France.

The prognosis for life is excellent. In no case has the disease itself caused death. Nevertheless, in isolated instances extensive ocular injuries occur. Also, as exemplified by the case reported, ankylosis and resultant limitation of function do occur.

The natural course of the disease is self limited, usually terminating in two to four months. However, relapses are not unusual and may occur over a period of many years. In Freund's case [41] a relapse occurred ten years after the onset of the illness, and the patient whose case I have reported had recurrences over the course of sixteen years.

ETIOLOGY AND EPIDEMIOLOGY

The cause of this syndrome is obscure. Almost as many etiologic agents have been indicated as there have been authors describing the

syndrome. High agglutination titers against dysentery organisms have led certain authors to consider them as causative agents,[27] although they were unable to culture the organism from the blood, stool or joint fluid. Anhemolytic streptococci have been found on blood culture,[4v] and the enterococcus has been held responsible by others.[4y] Atypical spirochetes were found in the blood by Reiter [28] and in the urethral discharge by Macfie.[3]

The most promising bacteriologic work has been done by Dienes,[29] who cultured pleuropneumonia-like organisms from the urethra of a man suffering from urethritis and arthritis. These organisms have previously been found in rats suffering from arthritis, in the conjunctival sac of normal mice and in agalactia in sheep, a syndrome consisting of conjunctivitis and arthritis and infection of the udders in the female and of the testes in the male. They have been cultured from the vagina of women suffering from leukorrhea and recently from the urethra of males suffering from nonspecific urethritis.[30] The organism is extremely pleomorphic, changes its shape and may reproduce by sexual and asexual means. In one form it may be filtered like a virus, and in another it may lead an intracellular, parasitic existence. In addition, forms exist which resemble true bacteria in every way, including growth requirements.[31]

When the drawings and description of the organisms found by Reiter [1] and Macfie [3] are compared with the known characteristics of the pleuropneumonia-like organisms, a striking resemblance is evident and suggests the possibility that they are, in fact, identical.

It is difficult to draw any conclusions as to the transmission of the disease in the general population. Cases in which diarrhea is present,

27. Fiessinger and Leroy.[2] Besson and Ehringer.[4c] Gounelle, Bohn, Koskas and Marche.[4d] Germain and Pirot.[4k] Hombourger (footnote 4 *l* and *m*). Kruspe.[4r] Rist.[4c'] Schittenhelm and Schlecht.[4f'] Schittenhelm.[4g'] Worms, Lesbre and Sourdille.[4p'] Worms and Sourdille.[4q'] Worms, Sourdille and Lesbre.[4r'] Worms, Lesbre and Sourdille.[4s']

28. Reiter (footnotes 1 and 4 *a'* and *b'*).

29. Dienes, L., and Smith, W. E.: Relationship of Pleuropneumonia-like (L) Organisms to Infections of the Human Genital Tract, Proc. Soc. Exper. Biol. & Med. **50**:99, 1942.

30. Beveridge, W. I. B.: Isolation of Pleuropneumonia-like Organisms from the Male Urethra, M. J. Australia **2**:479, 1943.

31. Beeuwkes, H., and Collier, W. A.: Studies on Arthrotropic Pleuropneumonia-like Microorganisms, J. Infect. Dis. **70**:1, 1942. Sabin, A. B.: Filterable Microorganisms of Pleuropneumonia Group, Bact. Rev. **5**:1, 1941. Shwartzman, G.: Some Recent Advances in Bacteriology and Virus Research with Special Reference to Electron Microscopy, J. Mt. Sinai Hosp. **11**:137, 1944. Dienes and Smith.[29] Beveridge.[30]

suggest entrance of the agent through the gastrointestional tract.[32] The causative agent may primarily damage the intestinal wall or may secondarily find a portal of entrance through the damaged mucosa, a mechanism which might be postulated in arthritides following ulcerative colitis and regional ileitis.

The available evidence indicates that in the nondiarrheal cases the genital tract is probably the channel of invasion.[33] The fact that the syndrome has never been reported in women does not eliminate this possibility. It is well known that the female genital tract harbors potentially pathogenic agents which never cause disease in the carrier [34] or cause at most a leukorrhea which is often overlooked or ignored.[4k] In this connection Kristjansen's experience [4q] is of great interest. In his patient nonspecific urethritis and arthritis developed one week following intercourse with a girl who was known to have a vaginal discharge which was repeatedly found negative for gonococci. She had relations with another man in whom a nonspecific urethritis without arthritis subsequently devoloped.

THERAPY

Practically all available types of medication has been used at one time or another, among them salicylates, arsenicals, mild mercurous chloride, fever therapy and, more recently, sulfonamide compounds and penicillin, all without success. For patients with gastrointestinal disturbances antidysentery serum has been tried. Usseglio and Zancan [18b] claimed some improvement with therapy with gold preparations. Kardung's [33b] patient was asymptomatic after three months following a course of systemic fever therapy.

SUMMARY

1. A case of Reiter's disease is presented which illustrates the different features of the disease.

2. The earliest symptom is frequently diarrhea followed by urethritis and conjunctivitis and later by migratory polyarthritis. Vesicular and hyperkeratotic cutaneous lesions are often noted. Infrequently bleeding tendencies with disturbances of the bleeding and clotting mechanism occur. Incomplete syndromes have been described.

32. Singer, G.: Die akute rheumatische Polyarthritis als Streptokokkenkrankheit, Med. Klin. **21**:1530, 1925. Pemberton.[24d]

33. (*a*) Frühwald, R., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 21, p. 487. (*b*) Kardung: Ein unter dem Bilde der Reiterschen Erkrankung verlaufender Fall von Urethritis, Arthritis und Conjunctivitis, Med. Welt **15**:403, 1941. (*c*) Beck.[4b] (*d*) Kristjansen.[4q] Kuske.[4s]

34. Hissard, R., and Husson, P.: Uréthrite vénérienne, subaiguë, bénigne, de nature inconnue, Bull. Soc. franç. der dermat. et syph. **39**:1877, 1932. Frühwald.[33a]

3. The disease occurs exclusively in males, usually in their early twenties.

4. It has been reported from Western Europe, the United States and the Pacific Islands.

5. The cause of the syndrome is obscure; the most likely etiologic agent belongs to the group of the pleuropneumonia-like organisms.

6. The portal of entry is either the gastrointestinal or the urethral tract.

7. The prognosis for life is good. Permanent ocular and joint lesions may occur.

Dr. Frederick Zak helped in the preparation of this paper.

CARDIAC ENLARGEMENT IN FEVER THERAPY INDUCED BY INTRAVENOUS INJECTION OF TYPHOID VACCINE

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THE effects of febrile illnesses on the heart have long been of interest to the physician. The pronounced weakness of the voluntary muscles in patients with infectious diseases suggests the possibility that the myocardium may also be affected. Observations that febrile illnesses rarely produce obvious signs of heart failure in otherwise normal subjects do not indicate that the heart remains unaffected. The myocardium of a normal person can withstand considerable strain and must be greatly injured before it will fail. Patients with infectious diseases are usually forced to remain at rest, and the great reserve of the heart is rarely exhausted. It has been noted, however, that in persons undergoing strenuous physical exertion cardiac enlargement frequently develops after intercurrent illnesses.[1]

In patients with subacute bacterial endocarditis cardiac decompensation has been precipitated by the intravenous injection of typhoid vaccine. We have also observed acute myocardial failure in a patient with induced malaria and hypertensive heart disease. That pneumonia and acute upper respiratory infections may initiate congestive failure in patients with compensated heart disease is well known.

In treating patients with neurosyphilis with fever induced by the intravenous administration of typhoid vaccine we have noted in roentgenographic examination that cardiac enlargement occurred in a significant number of cases. Our observations on this phenomenon constitute the subject of this report.

METHOD OF STUDY

Teleoroentgenograms of the heart were taken on 15 patients preceding fever, following each paroxysm and several weeks after the completion of therapy.

Aided by a grant from the Venereal Disease Division of the United States Public Health Service.

From the Departments of Roentgenology and Medicine (Clinic for Genito-infectious Diseases) of Grady Memorial Hospital and Emory University School of Medicine.

1. Kaufmann, R.: Ueber Herzerweiterungen, Wien. Arch. f. inn. Med. 1:211, 1920.

In a second group, of 24 patients, teleoroentgenograms were made before fever therapy and several months after its completion. In every repeat examination a special effort was made to obtain roentgenograms with the diaphragms in a position comparable to that of the original film; when this was not possible, the patients were excluded from the study. Deep inspiration was avoided to eliminate an involuntary Valsalva effect.

The size of the heart was determined in each roentgenogram by measuring the transverse diameter, since this seemed to be the simplest and most accurate method of obtaining comparable values. In normal patients the amplitude of the right border of the heart varies from 2 to 3 mm. and that of the left border from 3 to 5 mm.[2] Changes in the transverse diameter, less than 8 mm., therefore, were not considered significant in this study.

Electrocardiograms were taken frequently during the course of fever on 15 patients. Determinations of plasma protein were performed at weekly intervals by the falling drop method.[3] In 8 patients hepatic function was studied by the intravenous hippuric acid test before and after fever therapy. The right atrial pressure and the cardiac output were determined by the indwelling venous catheter technic on 8 patients at the completion of fever therapy.[4] Hematocrit readings and measurements of plasma volume were made before and after treatment in this group. The plasma volume was measured by the injection of the blue dye T 1824.[5] The concentration of dye was determined in a sample of serum obtained ten minutes after the injection of the dye.

Our method of producing hyperpyrexia in the treatment of neurosyphilis has been described in detail elsewhere.[6] In brief, the procedure consists in the administration of a series of continuous intravenous infusions of typhoid vaccine. A single treatment consists of approximately eight hours of fever (temperature 104 to 105 F.). Gradually increasing quantities of typhoid vaccine are given on alternating days until fifty hours of fever with temperatures above 103 F. are obtained. Temperatures higher than 106 F. are avoided whenever possible. During the febrile period not more than 4,000 cc. of fluid is given parenterally, half of which usually consists of isotonic solution of sodium chloride. Tolerance to the vaccine develops rapidly, and approximately 50,000,000,000 organisms are required to obtain a satisfactory febrile response by the time fever therapy is completed. The patients receive the regular hospital diet without additional vitamins or nourishment. During the febrile periods the patients are confined to bed, but they are ambulatory on the intervening days.

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2. Roesler, H.: Clinical Roentgenology of the Cardiovascular System, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1943.

3. Barbour, H. G., and Hamilton, W. F.: Blood Specific Gravity: Its Significance and a New Method for Its Determination, Am. J. Physiol. **69**:654, 1924.

4. Cournand, A.; Riley, R. L.; Breed, E. S.; Baldwin, de F., and Richards, D. W., Jr.: Measurement of Cardiac Output in Man Using the Technique of Catheterization of the Right Auricle or Ventricle, J. Clin. Investigation **24**:106, 1945.

5. Gibson, J. G., II., and Evelyn, K. A.: Clinical Studies of the Blood Volume: IV. Adaptation of the Method to the Photoelectric Microcolorimeter, J. Clin. Investigation **17**:153, 1938.

6. Heyman, A.: The Treatment of Neurosyphilis by Continuous Infusion of Typhoid Vaccine, Ven. Dis. Inform. **26**:51, 1945.

RESULTS

The results of the roentgenologic and laboratory studies on 15 patients during the period of fever therapy are shown in the table. Cardiac enlargement was noted in 8 cases, with increases in transverse diameter varying from 1 to 2.3 cm. (fig. 1 and 2). In 2 patients there was an associated pulmonary congestion, and in 2 others small areas of atelectasis developed. In 7 patients no significant enlargement of the heart was noted.

Only 1 patient (J. C., patient 3) was thought to have had preexisting heart disease. He gave a history of exposure to welding fumes, and the roentgenogram of the chest showed evidence of pulmonary fibrosis and slight prominence of the pulmonary artery. There were no murmurs, and the electrocardiogram showed right axis deviation. A diagnosis of early cor pulmonale was made.

The increase in size of the heart was usually recognized by the end of the first week, but it was more pronounced after the second or third week of therapy. Regression of the cardiac enlargement usually occurred during the month following fever.

In 9 of the 15 cases transient electrocardiographic changes were noted. These changes were slight, and they usually consisted of inversion of T waves or of slight elevation of the ST segment. No evidence of severe or permanent myocardial damage was noted. Following fever therapy a few rales were sometimes heard at the base of the lungs but these usually disappeared spontaneously. No changes were noted on auscultation of the heart. Pedal edema appeared occasionally after the patient left the hospital, but this was thought to be the result of hypoproteinemia. The majority of patients lost from 1 to 8 pounds (0.5 to 3.6 Kg.) in weight during the course of fever therapy. Five patients, however, gained from 3 to 6 pounds (1.4 to 2.7 Kg.).

The hemoglobin concentration and the hematocrit reading usually showed a pronounced fall. The changes in blood volume of the patients in whom cardiac enlargement developed were not consistent. Three of these patients showed increased blood volume, while the remaining patients showed decreased volume. The cardiac output and cardiac index were determined at the completion of fever therapy on 8 patients and were found to be within normal limits. One of these patients (patient 8) had an increase in atrial pressure.

The plasma protein levels were determined on 14 patients; the level was slightly elevated in 3 and significantly lowered in 11 patients. The hippuric acid excretion test showed impairment of hepatic function following fever therapy in 3 of the 8 patients tested.

In the second group of patients (24), teleoroentgenograms were obtained from three to twelve months after fever therapy was completed

Summary of Data for Fifteen Patients Before and After Fever Therapy

Patient No.	Initials	Age, Yr.	Sex	Race	Type of Neurosyphilis	Transverse Diameter of Heart, Cm.			Total Protein, Gm./ 100 Cc.		Hippuric Acid Test, Gm. Equivalent Benzoic Acid		Hematocrit, %		Blood Volume, Cc./Sq. M.		Cardiac Output, L./ Min.	Cardiac Index L./ Min./ Sq. M.	Electrocardiographic Changes
						Before Fever	After Fever	Change	Before Fever	After Fever	Before Fever	After Fever	Before Fever	After Fever	Before Fever	After Fever	After Fever	After Fever	
1	M. S.	30	F	N	Dementia paralytica	11.3	13.6	2.3	7.6	5.7	....	....	41.4	27.5	2,500	2,700	4.0	2.76	Inversion of T3
2	B. B.	25	M	W	Dementia paralytica	10.8	12.9	2.1	6.7	3.9	....	....	....	....	.....	.....	...	....	No change
3	J. C.	38	M	W	Optic atrophy	11.2	12.8	1.6	6.3	4.6	0.55	0.69	49.6	44.2	2,967	2,600	7.9	4.6	Slight elevation of ST3
4	L. K.	39	F	N	Optic atrophy	11.3	12.7	1.4	...	...	....	....	....	....	.....	.....	...	....	
5	J. C.	34	M	W	Tabes dorsalis	12.9	14.2	1.3	5.1	4.0	....	....	42.2	36.2	3,160	3,730	10.4	6.0	No change
6	G. A.	32	F	W	Asymptomatic	11.3	12.3	1.0	5.7	6.3	....	....	....	....	.....	.....	...	....	Inversion of T2 and T3
7	H. H.	40	M	N	Asymptomatic	13.8	14.8	1.0	6.8	7.3	....	....	....	....	.....	.....	...	....	No change
8	M. J.	27	F	N	Dementia paralytica	11.7	12.7	1.0	6.4	4.6	0.61	0.68	35.5	23.8	2,320	3,190	4.1	2.9	T1 and T2 became isoelectric
9	H. M.	34	M	N	Asymptomatic	16.2	17.0	0.8	5.4	4.2	0.80	0.24	47.9	41.0	3,520	3,380	6.4	3.5	Decreased voltage of T1 and T2
10	A. C.	27	F	N	Asymptomatic	14.5	14.7	0.2	5.8	5.1	0.93	0.75	41.4	33.0	2,300	2,540	5.5	3.5	No change
11	A. G.	30	F	N	Asymptomatic	9.7	9.5	0.2	6.0	4.8	0.59	0.72	34.6	22.9	2,100	2,600	5.4	3.6	No change
12	L. M.	36	F	N	Asymptomatic	13.1	13.2	0.1	7.5	5.8	....	....	....	....	.....	.....	...	....	Intraventricular conduction time increased to 0.06 second
13	A. F.	24	M	N	Asymptomatic	14.6	14.7	0.1	6.3	6.8	0.93	0.92	....	....	.....	.....	...	....	Changed to left axis deviation
14	M. P.	15	F	N	Optic atrophy	10.1	10.1	...	6.6	5.5	0.68	0.40	41.9	32.3	2,100	2,100	...	....	Inversion of T3
15	F. G.	29	M	N	Asymptomatic	12.2	12.2	...	6.7	5.7	1.0	0.50	43.5	38.5	2,200	2,500	4.95	3.1	Inversion of T3; elevated ST1 and ST2

and compared with those made before treatment. The heart was found to be larger in 4 patients, all of whom had had fever therapy within the preceding six months. In 4 additional cases definite cardiac enlargement was also present, but as these patients had gained considerable

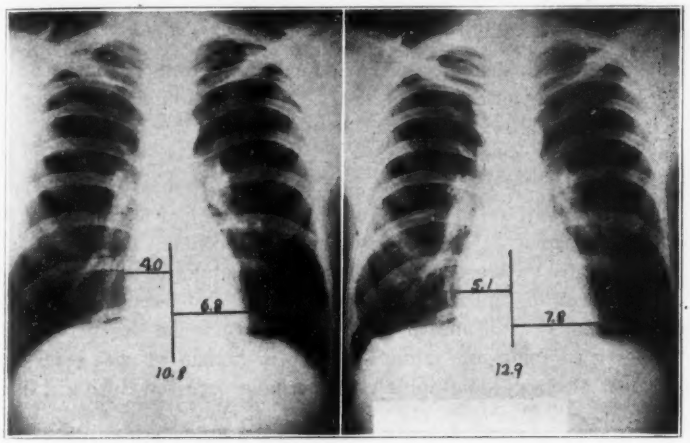

Fig. 1 (patient 2).—Cardiac enlargement. Roentgenograms of the chest taken before and after fever therapy. Note the small area of atelectasis in the base of the right lung.

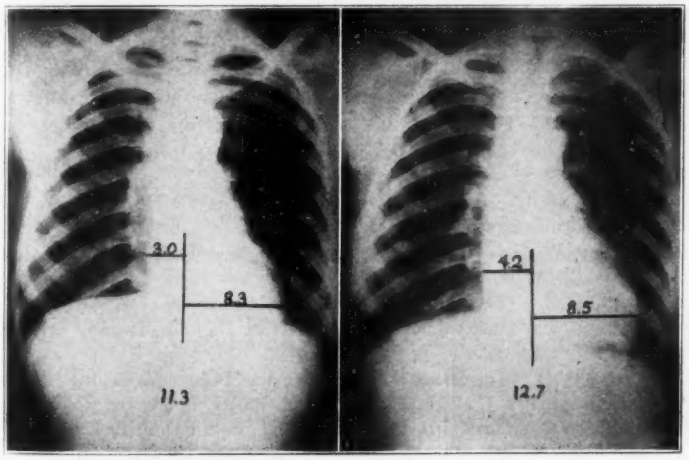

Fig. 2 (patient 4).—Cardiac enlargement. Roentgenograms of the chest taken before and after fever therapy.

weight the changes in heart size could not be evaluated. The remaining 16 patients showed no change in the cardiac silhouette. In no instance was the heart significantly smaller than before fever therapy.

COMMENT

The enlargement of the transverse diameter of the heart of 1 cm. or more represents a considerable increase in the total volume of the heart. An increase of only 0.5 cm. in transverse diameter of an average-sized heart has been shown to produce a 13 per cent increase in cardiac volume.[7]

Fever and febrile illnesses have for a long time been thought to exert a damaging effect on the heart. Thayer[8] found that 12 of 188 patients with typhoid fever had an increase in size of the heart on percussion three months to fourteen years after recovery from this infection. In a study of changes in the size of the heart in pneumonia Levy[9] noted that 60 per cent of the patients had roentgenographic evidence of cardiac enlargement during this infection. Both pneumonia and typhoid are known to produce histologic changes in the myocardium, and electrocardiographic abnormalities have also been noted during these infections.[10] In animal experiments myocardial degeneration has been observed following artificial fever; in human beings, severe and permanent electrocardiographic changes have occurred during artificial fever therapy.[11]

Despite these observations, little attention is generally paid to cardiac function in those febrile illnesses not primarily involving the heart. Since fever and febrile infections may exert a deleterious influence on the heart, their effects cannot be ignored.

The factors causing cardiac enlargement during febrile diseases have not been determined, and the few reports relative to this problem deal with avitaminosis or infections, such as diphtheria, which are known to affect the heart. Other possible sources of cardiac enlargement are: an increase in blood volume associated with acute infections; additional

7. Jonsell, S.: A Method for the Determination of the Heart Size by Teleroentgenography, Acta radiol. **20**:325, 1939.

8. Thayer, W. S.: The Late Effects of Typhoid Fever on the Heart and Vessels, Am. J. M. Sc. **127**:391, 1904.

9. Levy, R. L.: The Size of the Heart in Pneumonia: A Teleroentgenographic Study, with Observations on the Effect of Digitalis Therapy, Arch. Int. Med. **32**:359 (Sept.) 1923.

10. Stone, W. J.: The Heart Muscle Changes in Pneumonia, with Remarks on Digitalis Therapy, Am. J. M. Sc. **163**:659, 1922. Master, A. M., and Romanoff, A.: Electrocardiographic Changes in Pneumonia, Proc. Soc. Exper. Biol. & Med. **28**: 266, 1930. Brow, G. R.: The Heart in Typhoid Fever, Canad. M. A. J. **20**:606, 1929.

11. Haam, E., and Frost, T. T.: Changes in the Parenchymatous Organs, Produced by Artificially Induced Fever, Proc. Soc. Exper. Biol. & Med. **42**:99, 1939. Harvey, A. M., and Billings, F. T.: Coronary Occlusion After Fever Therapy for Sulfonamide-Resistant Gonorrheal Urethritis, Am. Heart J. **29**:205, 1945.

work placed on the heart by the heightened metabolism in fever; and, finally, direct injury to the myocardium produced by the infectious agent.

Influence of Blood Volume on Size of the Heart.—It has recently been suggested that cardiac failure in pneumonia or other infections is due in part to the increase in blood volume which has been described during these illnesses.[12] In view of the large quantities of fluids given parenterally to our patients undergoing fever therapy, this factor becomes of considerable interest. The effect of the circulating blood volume on cardiac size has been observed in a variety of diseases. The size of the heart is reduced in shock caused by decreased blood volume, and similar changes have been noted associated with acute hemorrhage.[13] The decreased size of the heart in Addison's disease has been attributed partly to the lower plasma volume occurring in this condition. As the blood volume is restored by the use of desoxycorticosterone in Addison's disease, the heart returns to its normal size. Occasionally an excess of desoxycorticosterone results in cardiac enlargement and pulmonary congestion.[14]

It was thought at first that a similar mechanism may have existed in our patients and that the enlargement of the heart was a result of an increased blood volume. Our studies failed to support this concept. The blood volume was slightly increased in almost every patient following fever, but there appeared to be no correlation between this fact and the changes in size of the heart.

In connection with this study, observations were made on 2 normal subjects as to the possible variation in cardiac size produced by sudden changes in venous pressure and by a rapid elevation of blood volume. The venous pressure and right atrial pressure were first lowered by the application of venous tourniquets to the thighs, and roentgenograms of the heart were made. The tourniquets were then released and 1,000 cc. of a 5 per cent solution of human albumin was given intravenously through a large bore needle and the roentgenograms of the heart repeated.

The application of venous tourniquets to the thighs would be expected to lower the atrial pressure by approximately 40 mm. of water. The

12. Rutstein, D. D.; Thomson, K. J.; Tolmach, D. M.; Walker, W. H., and Floody, R. J.: Plasma Volume and Extravascular Thiocyanate Space in Pneumococcus Pneumonia, J. Clin. Investigation **24**:11, 1945.

13. (*a*) Kondo, B., and Katz, L. N.: Heart Size in Shock Produced by Venous Occlusion of the Hind Limbs of the Dog, Am. J. Physiol. **143**:77, 1945. (*b*) Meek, W. J.: The Use of X-Rays in the Study of Physiology, Radiology **8**:369, 1927.

14. Ferrebee, J. W.; Ragan, C.; Atchley, D. W., and Loeb, R. F.: Desoxycorticosterone Esters: Certain Effects in the Treatment of Addison's Disease, J. A. M. A. **113**:1725 (Nov. 4) 1939.

rapid infusion of albumin would raise the atrial pressure approximately 100 mm. of water above the resting level. Thus the change in atrial pressure between the two roentgenographic examinations would be 140 mm. of water.[15]

As estimated from the change in hemoglobin concentration, the albumin had increased the blood volume by 1,150 cc. in subject 1 and by 1,000 cc. in subject 2 at the time the second films were taken. The change in venous pressure of 150 mm. of water and the increase of 1 liter in blood volume caused no significant increase in the size of the heart. In similar experiments on animals extremely large quantities of fluid by the parenteral route were necessary before cardiac enlargement occurred.[13b]

In the experiments recorded there was no change in the extracellular fluid volume, the entire change occurring in the atrial pressure and in the blood volume. It may be that an increase in blood volume associated with an increase in extracellular fluid volume would cause cardiac enlargement. This problem warrants further investigation.

It seems unlikely that the cardiac enlargement found in patients with febrile illnesses or in those undergoing fever therapy is caused exclusively by the relatively small increase of blood volume associated with these conditions. Further evidence against this possibility is the persistence in a few of our cases of cardiac enlargement for as long as several months, for usually the increase in blood volume produced by infections is temporary. [12]

Cardiac Work Produced by Fever.—The increase in metabolism produced by fever is to some extent covered by an increase in cardiac work. This factor must be taken into consideration, for increased work of the heart is known—in some athletes, for example—to produce enlargement. The few available reports on cardiac output during fever reveal that there is but little increase in cardiac output during fever or febrile infections.[16] In hyperpyrexia induced by short radio waves there is evidence that the cardiac output is definitely increased.[17] The influence of radiothermy on the circulation, however, is considerably different from that of other forms of fever, and a comparison of their effects on the cardiac output is not justified.[18]

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15. Stead, E. A., Jr., and Warren, J. V.: Unpublished data.

16. Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C Thomas, Publisher, 1932.

17. Kissin, M., and Bierman, W.: Influence of Hyperpyrexia on Velocity of Blood Flow, Proc. Soc. Exper. Biol. & Med. **30**:527, 1933.

18. Wiggers, C. H., and Orias, O.: The Circulatory Changes During Hyperthermia Produced by Short Radio Waves (Radiothermia), Am. J. Physiol. **100**: 614, 1932.

Nutritional Deficiency.—The possibility exists that the cardiac changes occurring in patients with febrile illness may be the result of nutritional disturbances. Our patients and persons with acute infections take little nourishment during the febrile period. As would be anticipated, considerable effect on both nitrogen balance and vitamin requirements occurs in these circumstances.

The increased utilization of proteins in febrile states is well known, and in some of our patients depletion of plasma proteins sufficient to produce edema developed. Depletion of protein in the body is known to produce dysfunction of many tissues, and it seems possible that the myocardium is also influenced by the destruction of protein in fever. The impairment of hepatic function in 3 patients in this series is of particular interest in this connection.

The increased metabolism in fever is associated with a greater vitamin requirement. It is possible that in our patients and in many of those with febrile infections, vitamin deficiencies similar to beriberi may develop. The onset of cardiac enlargement in our cases was relatively rapid, usually within the first week, and regression occurred without specific vitamin therapy. This seems to be evidence against avitaminosis as an important causative factor. It remains necessary, however, to study the effects of fever on patients having an adequate vitamin and protein intake.

Anemia.—In many persons with febrile conditions and in our patients undergoing fever therapy there is a decrease in the hemoglobin content and red blood cell count. Anemia is known to produce an added burden on the circulation and an increase in cardiac size. It is doubtful, however, whether the degree of anemia observed in our patients could play a predominant part in the production of cardiac enlargement.

Effect of Bacteria on Cell Metabolism.—It has been believed for a long time that cardiac failure in acute infections was due to direct injury to the myocardium produced by the infectious agent. It is conceivable, for instance, that the large quantities of typhoid vaccine used to produce fever in our patients may adversely affect the metabolism of the cardiac muscle. At the present time there is little information on this particular subject. Study of artificial fever therapy is indicated to determine whether cardiac enlargement is peculiar only to bacterial infections.

It may be that no one factor is entirely responsible for the cardiac enlargement observed in our patients. An increase in the blood volume by excessive parenteral administration of fluid, for example, produces little change in the normal heart. However, pulmonary congestion and cardiac failure have been noted following the parenteral administration of fluids to patients after operation or to those ill with acute infections. Similarly, it has been observed that in soldiers without preexisting heart disease cardiac enlargement was not likely to develop as a result

of physical exertion unless they were subjected to intercurrent infections.[1] It has also been shown that cardiac enlargement in beriberi occurs more often in those patients who have undergone physical stress.[19] Beriberi heart is also often precipitated by febrile illnesses. These clinical observations are of considerable importance and indicate the need for more intensive study of the effect of febrile illness on the heart.

SUMMARY

Enlargement of the heart has been noted by roentgenographic examination to occur during fever therapy in 8 of 15 patients with neurosyphilis. Roentgenograms of the heart were obtained on 24 additional patients who had undergone fever therapy during the preceding twelve months. In 4 of these patients, cardiac enlargement was present for as long as six months following hyperpyrexia.

Electrocardiographic studies and determinations of cardiac output, blood proteins and hemoglobin revealed no significant differences between the patients in whom cardiac enlargement developed and those without changes in size of the heart.

In our patients there appeared to be no relationship between the increase in cardiac size and the changes in blood volume. Evidence is produced to show that in normal subjects a rapid and significant increase in the circulating blood volume had no influence on cardiac size.

None of the factors known to influence cardiac size, such as anemia, nutritional deficiency or overwork of the heart, was thought to be the sole cause of the cardiac enlargement.

The observation that fever therapy produces an enlargement of the heart is of interest not only in the treatment of neurosyphilis but also in the consideration of the effects of febrile illnesses on cardiac function. The use of fever therapy provides an opportunity to study these effects under controlled conditions, and suggestions as to further investigation of this problem are offered.

Drs. E. A. Stead Jr., J. V. Warren and E. S. Brannon gave valuable assistance and advice in the preparation of this paper.

19. Aalsmeer, W. C., and Wenckebach, K. F.: Herz und Kreislauf bei der Beriberi Krankheit, Wien. Arch. f. inn. Med. **16**:193, 1929.

RHEUMATIC FEVER IN NAVAL ENLISTED PERSONNEL

I. An Analysis of the Major Manifestations Observed, the Factors Involved in Its Occurrence and the Cardiac Residua

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TWO hundred and twenty-one cases of rheumatic fever and rheumatic heart disease observed in this hospital have been analyzed in order to determine the significant factors involved in the occurrence of rheumatic fever in naval personnel, the clinical characteristics of the disease and the effectiveness of intensive salicylate therapy. The factors involved in its occurrence, the major manifestations observed and the incidence of permanent cardiac damage will be considered in this paper.

A significant difference exists between military and civilian population groups affected by rheumatic fever. The average age of onset in civilian life is 8 years, and 70 per cent of the persons affected have already acquired the disease by the age of 15.[1] A study of 1,000 cases followed for ten years by Bland and Jones[2] clearly indicates the outlook in this childhood group. The average age of onset was 8 years. Ten years later, at an average age of 18, when these persons would be acceptable for enlistment in the armed forces, 24 per cent were dead, 42 per cent showed varying degrees of permanent cardiac damage and only 31 per cent were free from cardiac lesions. Roughly, then, only 3 out of every 7 persons who have survived childhood rheumatic fever will be acceptable for military service.

No adequate information is available concerning the number of men with a childhood history of rheumatic fever serving in the armed forces. Master[3] found an incidence of 2 per cent among 432 surgical patients in a naval hospital. Two hundred neuropsychiatric patients questioned in this hospital by me revealed an incidence of 0.5 per cent. Delaney,

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writer and are not to be construed as reflecting the policies of the Navy Department.

1. (*a*) Cohn, A. E., and Lingg, C.: The Natural History of Rheumatic Cardiac Disease: A Statistical Study, J.A.M.A. **121**:1-8 (Jan. 2) 1943. (*b*) Coombs, C. F.: Rheumatic Heart Disease, Bristol, John Wright & Sons, Ltd., 1924.

2. Bland, E. F., and Jones, T. D.: Fatal Rheumatic Fever, Arch. Int. Med. **61**: 161-171 (Feb.) 1938.

3. Master, A. M.: The Problem of Rheumatic Fever in the Navy, Am. Heart J. **27**:634-640 (May) 1944.

Miller, Kimbro and Bishop [4] found 100 cases of valvular heart disease among 45,000 men examined for the Army Air Forces, all of whom had previously been screened by physical examination.

It may be assumed that between 5 and 20 men per thousand in the armed forces have had rheumatic fever before enlistment and that approximately 2 per thousand have rheumatic heart disease which existed prior to enlistment. With the exception of this small minority, service personnel should represent a population group from which persons highly susceptible to rheumatic fever have been eliminated.

MATERIAL AND METHODS

The 221 cases analyzed represent the consecutive patients with rheumatic fever and rheumatic heart disease admitted to a northwest naval hospital from December 1943 to April 1945. All patients admitted since January 1944 were under my direct supervision.

The case material was drawn from the Pacific Northwest and from evacuees from the Alaska-Aleutian, Central Pacific and South Pacific areas. Because of rapid movements of troops a patient's illness often had its inception in another geographic area, and the clinical data have been corrected accordingly. The home location of each patient represents the geographic area in which the maximum childhood and adolescent years were spent.

TABLE 1.—*Incidence of Cardiac Systolic Murmurs in One Hundred Neuropsychiatric Patients Considered as a Normal Control Group*

	Per Cent
Apical Murmurs	
Very slight systolic not transmitted	10
Slight systolic transmitted to anterior axillary line or farther	4
Basilar Murmurs	
Very slight systolic not transmitted	4
Slight systolic transmitted to neck	10
Slight systolic not transmitted	2

The assumption that rheumatic fever existed prior to enlistment is based on a definite history of growing pains with associated cardiac involvement, polyarticular arthritis, rheumatic carditis or chorea. Histories in all instances were obtained solely from the patient.

Cardiac murmurs were recorded as very slight, slight, moderate and loud. Mitral systolic murmurs were evaluated with the patient in the horizontal position and lying on the left side. One hundred neuropsychiatric patients, representing the same age groups, were examined under identical conditions in order to establish standards of expectancy for murmurs in normal persons. The results are presented in table 1. Only slight and very slight systolic murmurs were heard in this group. Slight mitral systolic murmurs transmitted to or beyond the anterior axillary line were found in 4 per cent, and no moderate mitral murmurs were heard.

4. Delaney, J. H.; Miller, S. I.; Kimbro, R. W., and Bishop, L. F., Jr.: Valvular Heart Disease Previously Unrecognized in Military Medical Examinations, J. A. M. A. **123**:884-886 (Dec. 4,) 1943.

Electrocardiograms were taken at weekly intervals. Deviations from normal were based on the criteria adopted by the American Heart Association. Blood sedimentation rates were determined twice weekly by the Cutler technic. A fall of 10 mm. or less in one hour was regarded as normal.

Patients with active rheumatic fever in this hospital were treated in most instances by the intensive salicylate method of Coburn.[5] Information is not available regarding prior treatment received by evacuees while at other hospitals; hence the possible influence of therapeutic procedures on the data to be presented is unknown.

Patients were kept under observation in this hospital until the rheumatic infection was quiescent or until chronic infection had persisted for more than three months. The shortest period of observation in cases of active disease was twenty-nine days, the longest two hundred and eighty-four days and the average fifty-eight days.

PRESENTATION OF DATA

1. *Clinical Manifestations of Rheumatic Fever Observed in Service Personnel.*—The major clinically recognizable manifestations of rheumatic fever consist of polyarticular arthritis, pains in the joints, chorea, valvular heart disease and carditis. In order correctly to evaluate the rheumatic fever problem as it exists in military personnel, it is necessary to establish the character and the incidence of these manifestations. This information, based on the 221 cases of rheumatic fever and rheumatic heart disease, is presented in table 2. One hundred and fifty-eight patients (groups I and II), or 71.4 per cent, 1 of whom had concurrent

TABLE 2.—*Major Rheumatic Manifestations Exhibited in Two Hundred and Twenty-One Patients Consecutively Admitted for Rheumatic Fever and Rheumatic Heart Disease*

Group	Rheumatic Manifestations Observed	Cases		Antecedent History of Rheumatic Fever
		No.	%	
I	Acute polyarticular arthritis with or without associated recognizable cardiac involvement	157	71.0	56 cases, preenlistment rheumatic fever; 1 case, preenlistment rheumatic fever and chorea; 13 cases, previous rheumatic fever in service but not prior to enlistment
II	Acute polyarthritis and Sydenham's chorea	1	0.4	Preenlistment rheumatic fever and chorea
III	Rheumatic heart disease and concurrent nondisabling pains in joints	12	5.4	6 cases, preenlistment rheumatic fever
IV	Rheumatic heart disease and concurrent chronic polyarthritis	5	2.0	Inception of rheumatic fever in childhood in all 5
V	Rheumatic carditis without other manifestations of rheumatic fever	10	4.6	No previous rheumatic fever
VI	Rheumatic valvular heart disease	36	16.6	14 cases, preenlistment rheumatic fever; 1 case, preenlistment and service rheumatic fever; 2 cases, rheumatic fever in service but not prior to enlistment

5. Coburn, A. F.: Salicylate Therapy in Rheumatic Fever: Rational Technique, Bull. Johns Hopkins Hosp. **73**:435-464 (Dec.) 1943.

Sydenham's chorea, exhibited acute polyarticular arthritis with or without cardiac involvement. An additional 17 patients (groups III and IV), or 7.4 per cent, exhibited articular manifestations in conjunction with rheumatic heart disease. The 5 patients (group IV) with chronic polyarthritis had articular manifestations of sufficient severity to necessitate hospitalization, but in some instances the diagnosis of rheumatic fever would not have been made except for the coexistent heart disease. The 12 patients (group III) with nondisabling pain in the joint represent a group who in many instances would either have remained on a duty status or have been disposed of in nonrheumatic fever wards except for the concurrent cardiac involvement. Therefore, the service incidence of chronic polyarthritis and nondisabling pain in the joint due to rheumatic fever is undoubtedly higher than the 7.4 per cent indicated in table 2, but a more accurate estimate cannot be established.

Most men with valvular heart disease were eliminated by enlistment physical examinations. Therefore, the incidence of 16.6 per cent is much lower than the 47 per cent observed by Cohn and Lingg [1a] in civilians of the same age group. In view of the fact that 40 per cent of these patients had experienced rheumatic fever prior to enlistment and that an appreciable number gave a history of heart disease prior to enlistment, the majority undoubtedly had their disease prior to enlistment and the cases do not represent instances of rheumatic fever acquired in service.

The incidence of carditis alone, without the other manifestations of rheumatic fever, was only 4.6 per cent, which coincides with the observations of Cohn and Lingg [1a] on civilians of the same age group. One patient had acute fulminating carditis and died on the fourth day of hospitalization. The remainder of the patients exhibited rheumatic fever of a relatively low grade activity which led to variable degrees of significant cardiac damage.

The tabulated data clearly indicate that the problem of rheumatic fever in service personnel consists primarily of the prevention, recognition and treatment of a disease which begins as acute polyarticular arthritis in at least 71 per cent of the cases and produces articular manifestations of some kind in over 79 per cent. Therefore, an analysis of the 158 cases (groups I and II) of acute polyarthritis observed during the acute, subsiding or convalescent phase, offered the best approach to the problem. The remainder of the clinical data are derived from this group.

2. *Preenlistment Rheumatic Fever.*—Forty-eight, or 36 per cent, of the group of 158 patients gave a history of rheumatic fever prior to enlistment. Of this number, 34 had had a single polyarticular episode, while 24 gave a history of two or more attacks. Nine of the latter group suffered from recurrent painful, and at times swollen, joints as often as two or three times a winter and/or from chronic residual pain

in the joints. One patient gave a history of chorea in addition to multiple attacks of polyarthritis.

Table 3 shows the age of onset in these patients. Seventy-one per cent had acquired the disease by the age of 15, which coincides with the general experience in civilian population groups.[1]

TABLE 3.—*Age at Beginning of Initial Attack of Fifty-Eight Patients Who Had Experienced Rheumatic Fever Prior to Enlistment*

Age, Years	Number of Cases	Per Cent Before and After Age 15
1- 5	5	71
6-10	18	
11-15	18	
16-20	13	29
21-25	3	
26-30	1	

The latent period between the last attack in civilian life and the first recrudescence in service is shown in table 4. If the 9 patients with chronic rheumatic infection are excluded, the latent period was more than five years in 67 per cent.

TABLE 4.—*Latent Period Before the Onset of the First Service Attack of Rheumatic Fever in Forty-Nine Patients Who Had Experienced Preenlistment Infection*

Latent Period, Years	Number of Cases *	Per Cent with Interval Less Than or More Than 6 Years
1- 5	16	33
6-10	19	67
11-15	8	
16-20	4	
21-30	2	

* Nine patients who experienced recurrent painful joints following the initial attack have been omitted.

3. *Preenlistment Home Area of Patients and Geographic Area in Which This Attack Began.*—The home areas of the patients who had a history of rheumatic fever prior to enlistment and those whose first attack began in service are presented in table 5. The influence of the location of this hospital in the Pacific Northwest is apparent in the data. Nevertheless, all sections of the country are represented. An appreciable number of the patients contracted preenlistment rheumatic fever in the Southeast and Southwest population areas, where the incidence of rheumatic fever is regarded as low.[6]

6. (*a*) Swift, H. F.: Public Health Aspects of Rheumatic Heart Disease, J. A. M. A. **115**:1509-1518 (Nov. 2) 1940. (*b*) Coburn, A. F.: The Factor of Infection in the Rheumatic State, Baltimore, Williams & Wilkins Company, 1931

(Footnote continued on next page)

Fifty-one per cent had lived in towns and rural and semirural areas, while 49 per cent lived in cities. The city-bred patients, better adjusted to the epidemiologic hazards of crowding, were as susceptible to service rheumatic fever as those from towns and rural and semirural areas.

The geographic area in which their attacks began is shown in table 6. The majority began in the Pacific Northwest. Nevertheless, all sections of the country were represented. A significant number contracted their initial infection or suffered recrudescence of quiescent infections

TABLE 5.—*Home Location of One Hundred and Fifty-Eight Patients with Rheumatic Fever*

Geographic Area of Home Location	First Attack Antedated Enlistment	First Attack in Service	Total
Northeast states	7	9	16
Southeast states	8	12	20
North-Central states	5	12	17
Central states	17	28	45
Northwest states	11	22	33
Southwest states	10	17	27
Total	58	100	158

TABLE 6.—*Geographic Area in Which This Attack of Rheumatic Fever Began*

Geographic Area in Which This Attack Began	Patients with Previous Rheumatic Fever	Patients Without Previous Rheumatic Fever	Total
Northeast states	2	3	5
Southeast states	1	0	1
Central states	2	1	3
Southwest states	5	6	11
Northwest states	43	59	102
Alaska-Aleutian area	8	11	19
Central Pacific area	9	6	15
South Pacific area	1	1	2
Total	71	87	158

in the Southwest, principally in San Diego, and in tropical areas where the incidence of rheumatic fever in civilian population groups is only one-fifth to one-fifteenth as common as in temperate zones of the United States.[7] In only 1 case was the disease incurred under the hardships of combat, which parallels observations from World War I that rheumatic fever occurred commonly in barracks-quartered troops but infrequently in troops in the field under combat conditions.[1b]

(*c*) Hedley, O. F.: Trends, Geographical and Racial Distribution of Mortality from Heart Disease Among Persons from 5-24 Years of Age in the United States During Recent Years (1922-1936), Pub. Health Rep. **54**:2271-2297 (Dec. 29) 1939.

7. (*a*) Clarke, J. T.: Geographical Distribution of Rheumatic Fever, J. Trop. Med. **33**:249-258 (Sept. 1) 1930. (*b*) White, P. D.: Heart Disease, ed. 2, New York, The Macmillan Company, 1937.

4. *Age when This Attack Began, Length of Service and Hereditary Factors.*—The age of onset of this attack is presented in chart 1.

The youngest patients were 17 years of age, and the oldest patient was 60. Forty-nine per cent were 18 to 20, which likewise represents the enlistment age of most recruits at the time of this study.

Chart 2 show the duration of service before this attack began.

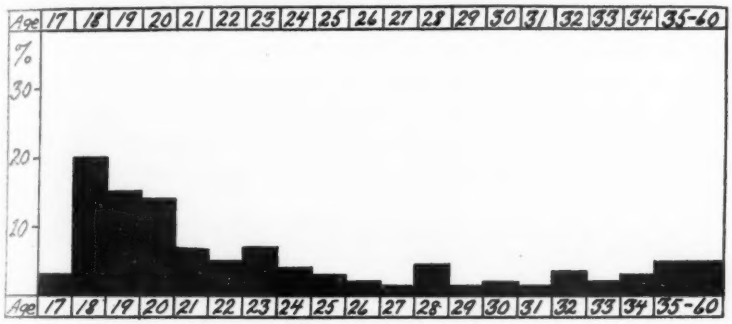

Chart 1.—Age at onset of the present attack of rheumatic fever (158 cases).

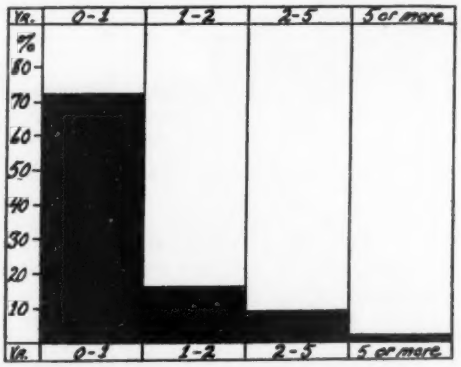

Chart 2.—Length of service before the beginning of the present attack of rheumatic fever (158 cases).

Since none of the patients who require hospitalization at primary training stations are admitted to this hospital, the number who contract rheumatic fever within the first year of service is actually higher than the 72 per cent occurrence rate shown in chart 2. Coburn [8] found that in 80 per cent of his cases the disease occurred in the first year. There-

8. Coburn, A. F.: The Management of Navy Personnel with Rheumatic Fever, U. S. Nav. M. Bull. **41**:1324-1328 (Sept.) 1943.

fore the high incidence of rheumatic fever in the 18 to 20 year old patients can be interpreted not as indicating unusal susceptibility at this age but, rather, as reflecting certain conditions inherent in the first year of service.

Hereditary factors were of no apparent significance. Only 8 per cent gave a family history of rheumatic fever.

5. *Seasonal Incidence of Rheumatic Fever.*—The seasonal trend under service conditions is presented in chart 3. Cases of patients received at this hospital through May 1945 have been included. The admission rate dropped materially after a large primary training center in the Northwest was closed, in the fall of 1944. Since then, the incidence of infection in early winter months has materially decreased and the seasonal trend more closely parallels the curve observed in civilian

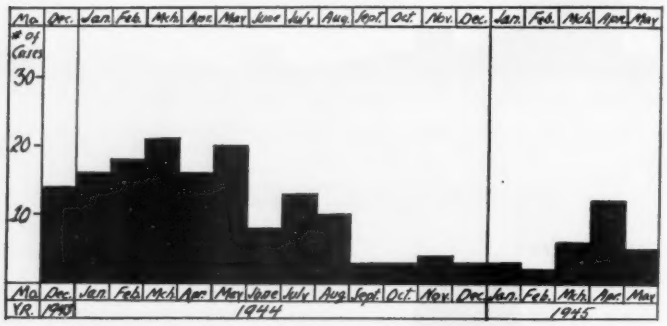
Mo.
Dec. Jan. Feb. Mch. Apr. May June July Aug. Sept. Oct. Nov. Dec. Jan. Feb. Mch. Apr. May
# of Cases
30
20
10
Mo.
Dec. Jan. Feb. Mch. Apr. May June July Aug. Sept. Oct. Nov. Dec. Jan. Feb. Mch. Apr. May
YR. 1943
1944
1945

Chart 3.—Seasonal distribution of cases of rheumatic fever from December 1943 to June 1945.

population groups,[7b] with the highest incidence in the late winter and spring months. As observed by others,[9] the service morbidity rate was low during the summer months.

6. *Relation to Antecedent Infections.*—Table 7 clearly demonstrates the striking relationship recognized as existing between antecedent infections of the respiratory tract and acute rheumatic fever in military as well as in civilian populations.[10] Of 81 per cent of patients who gave

9. Wendkos, M. H., and Noll, J., Jr.: A Survey of Rheumatic Fever in a Large Station Hospital, M. Clin. North America **28**:124-147 (Jan.) 1944.

10. (*a*) Coburn, A. F.: Observations on the Mechanism of Rheumatic Fever, Lancet **2**:1025-1030 (Oct. 31) 1936. (*b*) Jones, T. D., and Mote, J. R.: Clinical Importance of Infection of the Respiratory Tract in Rheumatic Fever, J. A. M. A. **113**:898-902 (Sept. 2) 1939. (*c*) Coburn, A. F.: Epidemiology of Streptococcus Hemolyticus Infections at Naval Training Stations, U. S. Nav. M. Bull. **41**:1012-1018 (July) 1943.

a history of antecedent factors, all except 3 per cent had infections of the respiratory tract, usually attributed to, or complicated by, hemolytic streptococci.

The time interval between the symptomatic onset of antecedent infections and rheumatic fever is shown in table 8. Only those patients

TABLE 7.—*Clinical Character of the Antecedent Illness Considered as Precipitating Rheumatic Fever (One Hundred and Fifty-Eight Cases)*

Antecedent Illness	Incidence, per Cent
Tonsillitis or sore throat alone or accompanied with other manifestations in the upper respiratory tract	46
Acute catarrhal fever	16
Cold in the head	8
Scarlet fever	5
Nasal infection	2.5
Otitis media	0.7
Acute gastroenteritis	1.4
Exposure	0.7
Diphtheria	0.7
No history of antecedent illness	19

who had a clearly defined onset have been included. An interval of one to three weeks existed in 43 per cent of the cases. In many instances the antecedent infection still persisted when the rheumatic fever began.

TABLE 8.—*Interval Between Symptomatic Onset of the Antecedent Infection of the Respiratory Tract and Rheumatic Fever*

Interval, Weeks	Per Cent of Cases
0-1	12
1-2	20
2-3	25
3-4	11
4-5	13
5-6	3
6-7	2
7-8	3
Recurrent infection over a period of 2-4 mo.	13

7. Residual Cardiac Observations.—The residual cardiac observations at the time of discharge from the hospital are presented in table 9. Seven per cent suffered permanent significant cardiac damage from this attack. Twenty-five per cent showed residual, slight or moderate apical systolic murmurs transmitted to or beyond the anterior axillary line, and they were classed as having potential rheumatic heart disease. Sixty-six per cent escaped any evidence of residual damage to the heart. Two patients with previous rheumatic heart disease showed evidence of further cardiac damage. All 13 of the patients who had experienced a previous attack in service but not prior to enlistment escaped residual significant heart disease.

The residual damage suffered from this attack consisted in 8 cases of mitral insufficiency, 4 with and 4 without roentgenic evidence of car-

diac enlargement; in 3 cases, of aortic and mitral insufficiency, 2 with and 1 without cardiac enlargement, and in 1 case of second degree cardiac enlargement with only a moderate mitral systolic murmur transmitted to the axilla. In 3 of the cases of mitral insufficiency there were middiastolic mitral murmurs in addition to the loud systolic murmur characterizing each of these cases. The evidence reported by Bland, White, and Jones[11] indicates that these cases should be classified as instances of mitral insufficiency rather than of early mitral stenosis. Of the 2 patients whose previous heart disease was aggravated, 1 showed mitral stenosis and aortic insufficiency with cardiac enlargement, and the other showed mitral stenosis without cardiac enlargement.

TABLE 9.—*Residual Cardiac Conditions in One Hundred and Fifty-Eight Cases of Acute Rheumatic Fever*

Group	Number of Patients	Heart Normal, %	Potential Rheumatic Heart Disease		Permanent Cardiac Damage, %	Rheumatic Heart Disease Existing Before This Attack but Aggravated by It, %
			SSM to A,* %	MSMM to A,† %		
Preenlistment rheumatic fever, single attack	34	62	12	14	8.5	3.5
Preenlistment rheumatic fever, multiple attacks	24	67	8	17	4	4
Previous attack in service but not prior to enlistment	13	77	7	16	...	...
First attack of rheumatic fever	87	65	12	13	8	...
Total	158	66	25		7	

* Slight systolic mitral murmur transmitted to or beyond the anterior axillary line.
† Moderate mitral systolic murmur transmitted to or beyond the anterior axillary line.

Abnormal electrocardiograms were encountered in 29, or 26 per cent, of the 113 patients observed during active infection. Fifteen, or 52 per cent, of this group showed no residual evidence of cardiac damage; 7, or 24 per cent, showed potential rheumatic heart disease, and the remaining 7, or 24 per cent, were among those who suffered permanent damage.

COMMENT

The clinical material presented clearly indicates that four major factors are involved in the occurrence of rheumatic fever in service personnel: (1) infections of the respiratory tract due to hemolytic streptococci, (2) length of service, (3) seasonal influences and (4) antecedent rheumatic fever. Seventy-eight per cent of the patients in this series gave a history of antecedent infection of the respiratory tract. The attack occurred within the first year of service in 72 per cent; the

11. Bland, E. F.; White, P. D., and Jones, T. D.: The Development of Mitral Stenosis in Young People, Am. Heart J. **10**:995-1004 (Dec.) 1935.

incidence was highest in winter and spring months, and 36 per cent had experienced rheumatic fever prior to enlistment. Other factors, including geographic origin of the patient, density of population of the home location, physical hardships related to service and hereditary background, were either of no significance or completely overshadowed.

Infections of the respiratory tract, length of service and seasonal influences are closely interrelated and reflect the epidemiology of hemolytic streptococcus infections of the respiratory tract. The close relationship between such infections and rheumatic fever is well recognized.[10] The 78 per cent incidence in this series of infections generally attributed to or complicated by hemolytic streptococci closely coincides with the 80 per cent incidence found by Coburn [10c] in naval personnel. Jones and Mote [10b] obtained a history of antecedent sore throats or colds in 63 per cent of a civilian group suffering from first attacks. Furthermore, the 37 per cent with a negative history showed immunologic evidence of a recent infection in most instances. Therefore, even though no symptomatic evidence exists, most first attacks can be attributed to recent hemolytic streptococcic infections.

Under the exigencies of war, the first year of service represents a phase of service life in which large numbers of unseasoned recruits are received at primary and secondary training centers where indoctrination and detachment occasion a rapid turnover of personnel. Few persons have a natural or acquired permanent immunity to hemolytic streptococcus infections.[12] Under these conditions, the major environmental factors favoring a high incidence of streptococcic infections of the respiratory tract are satisfied; namely, susceptibility of the host, high rate of change of population, overcrowding, widespread activity of a respiratory virus and the presence of one or more strains of hemolytic streptococci endowed with high communicability.[10c] Streptococcic infections of the respiratory tract, including scarlet fever, have been a serious problem in unseasoned recruits.[13] Therefore, it is not surprising that 72 per cent of the recruits susceptible to streptococcic infection acquired first attacks or recrudescences of preenlistment infection in the first year of service. The concentration of instances of rheumatic fever in the 18 to 20 year old group does not reflect an unusual susceptibility of this age group to the disease but reflects rather the age composition of the men exposed to the epidemiologic hazards of the first year in service.

12. Coburn, A. F., and Pauli, R. H.: Interaction of Host and Bacterium in Development of Communicability by Streptococcus Haemolyticus, J. Exper. Med. **73**:551-570 (April) 1941.

13. The Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine Prophylaxis in the United States Navy, United States Navy Department, Bureau of Medicine and Surgery, 1944.

Although only 5 to 20 men per thousand in the service population group had rheumatic fever prior to enlistment, this small group contributed 36 per cent of the 158 cases observed in this series. Master [8] found the even higher incidence of 54 per cent in a group of 80 persons who had rheumatic fever prior to enlistment, while Wendkos and Noll [9] reported 31 per cent and Jones [14] found that one third of the patients at Newport, R. I., training station had had rheumatic fever in childhood. An incidence of 30 to 36 per cent probably represents a more accurate estimate than the 54 per cent rate reported by Master.

Sixty-seven per cent of those with an infection prior to enlistment had been free from clinically recognizable infection for a period of six to thirty years (table 4). The observations of Wilson,[15] Keith [16] and Boone and Levine [17] clearly indicate that only a small minority experience recurrences after puberty and after freedom from infection for more than five years in a civilian environment. Therefore, most of this group would have escaped recrudescences in civilian life. Yet under service epidemiologic hazards this group alone contributed 33, or 21 per cent, of the 158 cases.

The occurrence of 7 first attacks and 10 recrudescences in the tropics reflects certain exigencies of military life already touched on rather than the inherent rate for rheumatic fever in tropical areas. This is borne out by the fact that 14 of the 17 cases occurred in the Hawaiian area, where large numbers of new arrivals are constantly received from the United States and transshipped to other areas. Furthermore, primary training stations located in North Carolina, Louisiana and California, where climatic conditions are favorable, experienced a high weekly morbidity rate of over 20 cases expressed in annual admission rates per thousand strength during the winter of 1944. Thus, under the exigencies of war, climate alone will not eliminate the hazard of service rheumatic fever.

Only 18 per cent of the 158 cases of acute polyarticular arthritis developed in the tropics, while 75 per cent of the 12 cases characterized by nondisabling pains of the joints and valvular heart disease began there. This would indicate that, as in civilian population groups,[6a]

14. Quoted by Master.[8]

15. Wilson, M. G.: The Natural History of Rheumatic Fever in the First Three Decades, J. Pediat. **10**:456-465 (April) 1937.

16. Keith, J. D.: Observations on Diagnosis and Treatment of Rheumatic Heart Disease, Practitioner **151**:38-42 (July) 1943.

17. Boone, J. A., and Levine, S. A.: The Prognosis in "Potential Rheumatic Heart Disease" and "Rheumatic Mitral Insufficiency," Am. J. M. Sc. **195**:764-770 (June) 1938.

a larger proportion of cases occurring in tropical areas will exhibit mild polyarthritis than those occurring in temperate zones, and the problem of accurate recognition is enhanced.

The 7 per cent incidence of significant residual cardiac damage in patients who were free from heart disease before the present attack is considerably lower than the incidence in children [18] but it coincides with the observations of DeLiee, Dodge and McEwen [19] concerning civilians 25 years of age or older. As already stated, most patients with active infection in this hospital were treated by the intensive salicylate regimen which Coburn [5] found prevented significant cardiac residua. Those who were free from clinically recognizable carditis when therapy was instituted in this hospital escaped residual damage, but residual stigmas were not prevented in patients who already exhibited significant carditis before treatment was begun. Since the treatment regimen before admission to this hospital is unknown in most instances, the possible influence of Coburn's intensive salicylate regimen on the data presented cannot be estimated.

Some of the patients who escaped with normal hearts, had clinical and/or electrocardiographic evidence of carditis during the active phase of infection. This regression of clinical and electrocardiographic signs of carditis is a common observation. Furthermore, this favorable sequence of events occurred in 8.3 per cent of 1,000 children and adolescents stigmatized with rheumatic heart disease who were observed over a ten year period by Bland, Jones and White.[18] Therefore, the possibility exists that further regression of physical signs may occur in the 7 per cent in this series classed as suffering permanent significant cardiac damage from this attack.

The outlook for the patients who were entirely free from residual evidence of heart disease or classed as having potential rheumatic heart disease can be considered favorable. Bland and Jones [20] found that characteristic signs of permanent valvular deformity, not present at the time of the original illness, developed in 25 per cent of 314 children observed over a ten year period. This so-called delayed appearance was clearly associated with coexisting signs of recurrent rheumatic fever in two thirds of the group, while in the remaining one third it occurred insidiously. Boone and Levine [17] found the outlook was much more

18. Bland, E. F.; Jones, T. D., and White, P. D.: Disappearance of the Physical Signs of Rheumatic Heart Disease, J. A. M. A. **107**:569-573 (Aug. 22) 1936.

19. DeLiee, E. F.; Dodge, K. G., and McEwen, C.: The Prognostic Significance of Age at Onset in Initial Attacks of Rheumatic Fever, Am. Heart J. **26**:681-684 (Nov.) 1943.

20. Bland, E. F., and Jones, T. D.: The Delayed Appearance of Heart Disease After Rheumatic Fever, J. A. M. A. **113**:1380-1383 (Oct. 7) 1939.

favorable in an intermediate age group, averaging 13.8 years of age and observed for 9.5 years; in only 4.8 per cent of 166 patients with a history of rheumatic fever or chorea but with either a normal heart or a systolic murmur of not more than grade 1 intensity did signs of valvular deformity subsequently develop. Bland and Jones [20] have expressed the opinion that the considerable difference in the incidence of delayed heart disease in the two groups reflects the milder character of rheumatic fever in the second decade of life in contrast to the first. Therefore, the 93 per cent of service patients who escape significant residual cardiac damage, many of whom are already in the third decade of life, should face minimal danger of delayed valvular heart disease in subsequent years in terms of a civilian environment. The prognosis under the increased epidemiologic hazards of continued service cannot be estimated.

CONCLUSIONS

1. Polyarticular arthritis is the major rheumatic manifestation witnessed in service personnel and occurs in the acute form in 71 per cent and in some form in 79 per cent of the cases. The incidence of carditis without articular manifestations is 4.6 per cent and of valvular heart disease is 16.6 per cent. In most of the cases of the latter group the disease existed prior to enlistment and does not reflect service rheumatic fever.

2. Rheumatic fever noted during military service occurs in tropical and subtropical as well as in temperate zones. A greater percentage of military personnel experience mild polyarthritic manifestation in tropical areas, complicating the problems of diagnosis.

3. Four major factors are involved in the occurrence of rheumatic fever in military personnel: (1) streptococcic infections of the respiratory tract; (2) length of service; (3) seasonal influences, and (4) antecedent rheumatic infection. Infections of the respiratory tract, length of service and seasonal influences are closely interrelated and reflect the epidemiologic hazards of hemolytic streptococcus respiratory infections in the first year of service.

4. Although only 5 to 20 per thousand persons in the service population have suffered from rheumatic fever prior to enlistment, this small minority accounts for 30 to 36 per cent of rheumatic attacks during military training.

5. Significant residual cardiac damage which had not existed previously occurred in 7 per cent of 158 patients with acute polyarticular rheumatic fever. Sixty-six per cent escaped with normal hearts. Twenty-five per cent showed residual slight or moderate systolic mitral murmurs transmitted to or beyond the anterior axillary line, and they were classed as having potential rheumatic heart disease. It seems likely

that less than 5 per cent of the patients who escaped with normal hearts or were classed as having potential rheumatic heart disease face the prospect of delayed significant cardiac residua in a civilian environment, but the prognosis under the increased epidemiologic hazards of continued military service cannot be estimated.

6. Abnormal electrocardiograms were encountered in 26 per cent of the 113 patients observed during active infection. Only 24 per cent of this group showed residual physical signs of significant cardiac damage.

Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

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THE material for this article has been selected from publications which have appeared from July 1944 to June 1945. In this review [1] especial emphasis is placed on subjects of particular current importance, e. g., biologic false positive reactions to serologic tests for syphilis and new methods of treatment, especially with penicillin, though articles on other important subjects are not neglected. The number of European journals available for review is negligible.

EXPERIMENTAL SYPHILIS

Chesney and Woods [2] report experiments to determine the extent to which a primary syphilitic infection of the cornea in rabbits is followed by the development of a local corneal immunity, by the generalized spread of Treponema pallidum and by the development of a general

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1. (*a*) Moore, J. E.: Syphilis: A Review of the Recent Literature, Arch. Int. Med. **56**:1015 (Nov.) 1923. (*b*) Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **58**:901 (Nov.) 1936; (*c*) **60**:887 (Nov.) 1937. (*d*) Padget, P.; Sullivan, M., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **62**:1029 (Dec.) 1938. (*e*) Moore, J. E., and Mohr, C. F.: Syphilis: A Review of the Recent Literature, ibid. **64**:1053 (Nov.) 1939. (*f*) Mohr, C. F.; Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **66**:1112 (Nov.) 1940. (*g*) Mohr, C. F.; Padget, P.; Hahn, R., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **69**:470 (March) 1942. (*h*) Reynolds, F. W.; Mohr, C. F., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **70**:836 (Nov.) 1942; (*i*) **72**:635 (Nov.) 1943. (*j*) Mohr, C. F.; Scott, V.; Hahn, R. D.; Clark, E. G., and Moore, J. E.: Syphilis: A Review of the Recent Literature, Arch. Int. Med. **74**:390 (Nov.) 1944.

2. Chesney, A. M., and Woods, A. C.: Further Observations on the Relation of the Eye to Immunity in Experimental Syphilis: II. The Development of Immunity After Primary Intracorneal Inoculation, J. Exper. Med. **80**:357 (Nov.) 1944.

immunity to the infection. Female rabbits were inoculated intracorneally with a virulent strain of T. pallidum, and the disease was allowed to run its course until the lesions which had developed at the site of inoculation had healed spontaneously. Popliteal lymph nodes transferred from about one half of these animals to normal male rabbits proved in almost every instance to contain virulent spirochetes, showing that generalization of the syphilitic infection is the rule after intracorneal inoculation. All animals were treated with arsphenamine after the local lesion had subsided. The rabbits were then reinoculated with the homologous strain of spirochetes, injections being made into the cornea originally inoculated and also into the skin of the back. In one experiment both corneas were reinoculated.

The incidence of lesions developing in either cornea after reinoculation was higher than the incidence of lesions developing in the skin. The lesions developing in the corneas of the "immune" animals had a longer period of incubation and were of shorter duration on the average than the lesions in the control group. Inoculation of the cornea of rabbits with T. pallidum is often followed by the development of immunity to the homologous strain of organisms. This immunity is imparted to the skin to a greater extent than to either the cornea inoculated originally or the opposite uninoculated cornea. It persists after treatment with arsphenamine. It appears to be more marked the longer treatment is postponed.

In another paper, Chesney and Woods [3] report further observations on the relation of the eye to immunity in experimental syphilis. Two experiments were conducted in which rabbits originally inoculated with syphilis and treated late in the course of the disease (one hundred and seventy-fourth to two hundred and tenth day) were reinoculated subsequently in both corneas with the homologous strain of spirochetes. In each animal one cornea had been previously inoculated with dead tubercle bacilli. This procedure was carried out in order to bring about a nonspecific inflammatory reaction with resultant vascularization, the intention being to determine whether vascularization would render the cornea more resistant to reinoculation with T. pallidum. The results of both experiments were inconclusive though similar.

While in the immune animals the behavior of the left corneas (into which dead tubercle bacilli had previously been injected) toward a second inoculation with a homologous strain of T. pallidum did not differ sharply from that of the right corneas, which had not been rendered

3. Chesney, A. M., and Woods, A. C.: Further Observations on the Relation of the Eye to Immunity in Experimental Syphilis: III. The Influence of a Non-Specific Inflammatory Reaction in the Cornea on the Development of Immunity in That Tissue After Intratesticular Inoculation, J. Exper. Med. **80**:369 (Nov.) 1944.

vascular by the injection of the bacilli, nevertheless the same trend was observed in each experiment. This trend was toward a greater resistance to a second inoculation with homologous syphilitic virus on the part of the vascularized left corneas. This might theoretically be due to one of two factors: (a) exposure of the corneal cells to a greater amount of antigen brought to them by the new vessels in the cornea, with a resultant active cellular response, or (*b*) the presence of an increased amount of circulating humoral antibodies.

Wile and Johnson [4] undertook experiments to determine the usefulness of white mice as carriers of syphilitic infection, and whether after inoculation T. pallidum survived in the spiral form or whether evidence could be found of a granular or infravisible form. They inoculated three groups of animals with the Nichols strain of T. pallidum. In one group they introduced the inoculum intraperitoneally, in the second group intracranially and in a third group intracutaneously, utilizing a previously produced marsupial pouch. Similar inoculations were carried out on splenectomized and on nonsplenectomized animals. After forty-eight to one hundred days the organs of the inoculated mice were ground up and injected into rabbit testes. In rabbits inoculated with organs from all three groups of mice typical testicular syphilomas developed. The infection was as readily conveyed from mouse tissue in splenectomized as in nonsplenectomized animals. Despite repeated efforts to demonstrate the spiral form of the organisms by dark field and tissue-staining technics, none was found in the mouse inoculums which resulted in infection in rabbits. Furthermore, no histologic changes suggestive of syphilis could be demonstrated in any of the mouse tissues examined. These facts led Wile and Johnson to believe, with certain earlier workers, that an infectious granular or infravisible form of the spirochete of syphilis does exist.

SERODIAGNOSIS OF SYPHILIS

Quantitative Serologic Tests.—Heyman [5] reemphasizes the value of quantitative serologic tests for syphilis in selected cases. With the aid of case reports, he points out the worth of serial determination of serum reagin in the diagnosis of primary syphilis when results of repeated dark field examinations are negative and discusses the detection of early congenital syphilis, the recognition of relapse in early syphilis following treatment, the differentiation of seroresistance from serologic

4. Wile, U. J., and Johnson, S. A. M.: The Use of Splenectomized and Nonsplenectomized Mice in the Production of Experimental Syphilis in Rabbits, Am. J. Syph., Gonor. & Ven. Dis. **28**:422 (July) 1944.

5. Heyman, A.: Quantitative Serologic Tests for Syphilis, New England J. Med. **232**:124 (Feb. 1) 1945.

relapse, the detection of the prozone phenomenon and the serologic follow-up of patients suspected of having biologic false positive reactions.

BIOLOGIC FALSE POSITIVE REACTIONS TO SEROLOGIC TESTS FOR SYPHILIS

Davis [6] has written a comprehensive article on the subject of biologic false positive reactions to serologic tests for syphilis with an exhaustive review of the literature. He summarizes as follows:

The serologic tests for syphilis are subject to marked variations in sensitivity; these largely account for the discrepancies in published reports on the incidence of biologic false positive tests in various diseases. Many of the cases reported have undoubtedly been technical false positives based on unreliable earlier Wassermann tests. Standards of performance of Wassermann (complement fixation) and flocculation tests have been elevated by international and United States Serologic Evaluation Surveys, but fluctuation in day to day results on weakly positive sera is still inevitable. In order to avoid technical false positive reactions, it is desirable to obtain more than one positive test before considering a case biologic false positive.

The incidence of transient positive tests following acute infections depends largely on the frequency of testing during the acute and convalescent stages. Although post-infectious or post-vaccinial positive reactions occasionally last as long as 3 months, most become negative within a few days or weeks. Since it is customary to perform serologic tests on hospital patients only on admission, at which time acute infections have not fully developed their antibodies, it is likely that the ability of many common infections to lead to false positive serologic tests is grossly underestimated. Those causes of transient positive reactions (malaria and vaccination) which have been tested at short intervals have shown some degree of reaction in nearly 100% of the cases, but the majority of these were only 1 or 2 plus reactions, and would ordinarily be reported as negative or doubtful. Similar studies would be desirable in a variety of common infectious diseases.

False positive serologic tests are common (more than 10% of cases) in leprosy, malaria in the acute stages, infectious mononucleosis, vaccination against smallpox, rat-bite fever due to Spirillum minus, relapsing fever, lupus erythematosus, and possibly certain types of atypical pneumonia. There is no reliable evidence that the serologic tests are significantly affected by pregnancy, menstruation, scarlet fever, jaundice (other than infectious), subacute bacterial endocarditis, tuberculosis, or hyperproteinemia, in spite of earlier reports. Inadequate data are available on measles, mumps, infectious hepatitis, lymphopathia venereum, chancroid, and many other diseases.

Transient false positive reactions may occur in apparently normal individuals without recent illness, and in cases of some diseases in which the incidence is so low as to suggest that the relationship may be coincidental. It has recently been suggested that even persistently positive reactions may occur in non-syphilitic patients. Since a large proportion of seropositive patients have no syphilitic lesions at autopsy, it is entirely possible that many seropositive persons without a history or signs of the disease have been mistakenly diagnosed and treated for latent syphilis. Surveys of normal populations have shown that the incidence of false

6. Davis, B. D.: Biologic False Positive Serologic Tests for Syphilis, Medicine **23**:359 (Dec.) 1944.

positive reactions is only a small fraction of 1%, but in large serologic dragnets the number of innocent victims may be large, and the psychological, social, and legal consequences to the individual may be serious.

Since low titer syphilitic sera may show discrepancies between the results obtained with various test antigens, and fluctuation in apparent reactivity of successive sera, these are not adequate criteria for considering a positive serum false. . . .

Some of the false positive reactions may be eliminated in the future by purification and improvement in specificity of lipid antigens of the Wassermann group, but there is no reason to expect all false Wassermann antibodies to differ in any given respect from the true antibody. Attempts to find consistent empirical physico-chemical differences between syphilitic and false positive sera have thus far failed. To the reviewer [Davis] the most promising approach to the problem is the detection of antibodies to antigens of the spirochete other than Wassermann antigen. Although virulent Treponema pallidum has not yet been cultivated, certain strains of cultured spirochetes have been found to be antigenically distinct from Wassermann antigen in the complement fixation test, and to detect syphilitic sera with encouraging regularity. The specificity of such a spirochetal antigen was found in the 1941 U. S. Serologic Evaluation Survey to be too low to permit its use as a serodiagnostic procedure, but this does not eliminate its potential value as a verification test. Further work is indicated.

. . . A positive serologic test is not an emergency. The most important procedure, in the absence of pregnancy, is a probationary period of at least 3 months before starting treatment. While many false positive tests will be revealed as transient during this period, there are no verification tests available today to help in the diagnosis of those which remain positive.

Fractionation of Serum Globulin.—Neurath and his associates [7] publish a preliminary communication concerning an important and extensive study directed toward the development of a serodiagnostic method for the differentiation between syphilitic serums and those which give biologic false positive reactions. They believe that in these two groups of serums the reactive antibodies differ from each other in certain significant respects. Serums from patients with syphilis differed noticeably from normal serums, exhibiting electrophoretically decreased albumin and increased gamma globulin contents. The difference is both relative and absolute. Serums with biologic false positive reactions from presumably normal persons showed differences from normal serums qualitatively similar to those of syphilitic serums but of considerably smaller magnitude. However, serums with biologic false positive reactions from persons known to have diseases other than syphilis gave electrophoretic results essentially like those obtained with syphilitic serums.

When the various components of the serum were separated by either of two alternative chemical methods of fractionation, it was found

7. Neurath, H.; Volkin, E.; Erickson, J. O.; Putnam, F. W.; Craig, H. W.; Cooper, G. R.; Sharp, D. G.; Taylor, A. R., and Beard, J. W.: The Serological Diagnosis of Syphilis, Science **101**:68 (Jan. 19) 1945.

that fractions G I and G II contained most of the serologic activity, whereas crude albumin was always serologically inactive. The sum total of the individual titers of the isolated fractions of the syphilitic serums was consistently less than that of whole serums, whereas with serums giving biologic false positive reactions elimination of crude albumin resulted in a significant increase in the titer of the globulins over that of the parent serums. This differential behavior, particularly pronounced with weakly reactive serums, suggested an inhibitory effect of crude albumin on the reaction of antibodies of serums having biologic false positive reactions with lipoidal antigen.

It was further found that addition of the crude albumin fraction to globulin fractions derived from serums with false positive reactions caused complete inhibition of specific flocculation with lipoidal antigen, as well as redispersion of floccules formed before crude albumin was added. This inhibitory phenomenon did not, however, occur when a test was made with globulins isolated from syphilitic serums. The inhibitor has not yet been isolated and identified, but work is in progress toward this end.

Neurath and his group have demonstrated that the antibodies of serums with false positive reactions are more susceptible to inactivation by heat than those of syphilitic serums. Finally, they have achieved a considerable degree of concentration of the syphilitic antibody by adsorption from whole serums on freshly precipitated calcium phosphate followed by precipitation of the eluate with ammonium sulfate. Their observations "indicate that the antibodies of truly syphilitic sera, reactive with lipoidal antigen, differ from those of biologic false positive sera in certain chemical and immunological respects. The possibility of the application of these findings to the development of a practical method of differentiation is being explored."

To the reviewers this work of Neurath and his associates seems the most promising present avenue of approach toward solution of the difficult problem of serologic recognition of biologic false positive reactions to serologic tests.

Cooper [8] reports the result of electrophoretic analysis of syphilitic serums under varying conditions. Two strongly seropositive serums from patients with clinical syphilis were studied. Inactivation by heating to 56 C. for thirty minutes produced no significant change in the distribution of the electrophoretic fraction. Flocculation with Kahn antigen resulted in a decrease in gamma globulin. This suggests that reagin is associated with this fraction. When electrophoretic analyses and serologic tests were performed on protein fractions obtained by

8. Cooper, J. A.: Identification of Serum Fraction Carrying Syphilitic Reagin by Electrophoresis, Proc. Soc. Exper. Biol. & Med. **57**:248 (Nov.) 1944

salting out with ammonium sulfate, reagin appeared to be associated with the beta or gamma globulin fractions or with both.

In another experiment, Cooper [9] studied by electrophoresis serums from 13 patients with various types of syphilis. Although the total protein concentrations in these serums were within the normal range, there was characteristically a decrease in the albumin concentration and an increase in all three globulin fractions. According to Cooper, this change in the serum protein picture occurs soon after infection with syphilis and persists throughout the course of the disease in the absence of adequate treatment. There was no apparent correlation between the quantitative Kahn titer and the increase in concentration of the total globulin or of any electrophoretic fraction. Gamma globulin was the fraction with which syphilitic reagin appeared to be associated. In 5 patients suspected of having biologic false positive reactions the characteristic changes found in syphilis did not occur.

Kahn and McDermott [10] report that among 1,400 recently inducted Naval personnel 69 were found to have positive Kahn reactions of intensities ranging from doubtful to 4 plus. Sixty-seven of these positive reactions, studied by Kahn's "verification" technic, were biologic false positive results. It was later learned that the donors of these 67 blood specimens had been vaccinated against smallpox about two months previously. In follow-up Kahn tests of 45 of the 67 seropositive nonspecific reactors reactions became negative in all but 4, who later reverted to seronegativity after an interval of two months. These results indicate to the authors that false positive reactions are detectable by means of the Kahn "verification" test. It has not yet been shown, however, that Kahn's misnamed test can actually differentiate or "verify" the positive results obtained in syphilis and other conditions.

Escobar [11] concludes that the Kahn "verification" test is of no value in differentiating between pinta and syphilis.

Rein and Elsberg [12] provide a comprehensive discussion of "verification" tests in the serodiagnosis of syphilis and conclude that none of these methods so far devised, including that of Kahn, can distinguish consistently between true and false positive reactions. They suggest that any new "verification" test should be subjected to critical evalua-

9. Cooper, J. A.: An Electrophoretic Study of Syphilitic Sera, J. Invest. Dermat. **6**:109 (April) 1945.

10. Kahn, R. L., and McDermott, E. B.: The Verification Test in Post-Vaccination Cases, J. Bact. **47**:460 (May) 1944.

11. Escobar, J. J.: The Reaction of the Kahn Verification Test in Pinta, Bol. clín., Univ. de Antioquia **6**:543 (Nov.) 1940.

12. Rein, C. P., and Elsberg, E. S.: Are Current Verification Tests of Practical Value in the Serodiagnosis of Syphilis? J. Invest. Dermat. **6**:113 (April) 1945.

tion by a selected committee of serologists and clinicians before it is released for general clinical use.

Biologic False Positive Tests in Malaria.—Rosenberg [13] aimed to determine which of several serologic tests for syphilis gave the least proportion of falsely positive reactions in patients with malaria and whether it was possible to distinguish malaria from syphilis on the basis of definite patterns of positivity among the different tests. He found that cases of mixed infections (Plasmodium falciparum and Plasmodium vivax) gave the highest incidence of positive results with all tests. Plasmodium malariae infections were not included in this study. The "strongest positive" reactions were obtained between seven and ten days after the first chill and persisted for from four to six weeks. The serologic reactions tended to remain positive longer in case of infections with P. falciparum. When parasites persisted despite the lack of clinical evidence of malaria, the falsely positive reactions remained at a high level. Fever per se could not be correlated with positive reactions. A characteristic pattern of positivity was found in most malarial serums. Generally the Kahn and Mazzini flocculation tests elicited positive reactions, the Kolmer complement fixation positive or doubtful reactions, the Kline flocculation test doubtful or weakly positive reactions and the Eagle and Hinton flocculation tests negative reactions or reactions which if positive soon reverted to negative.

Potter and his co-authors [14] have attempted to discover the effects of malaria on the reaction to the Wassermann test of the spinal fluid. From 100 consecutive patients with malaria specimens of blood and spinal fluid were taken within forty-eight hours of their entrance into the hospital. With the exception of 1, all had infections with P. vivax. These 100 patients gave no history of syphilis, and none had previously had such a diagnosis. Those who had positive or doubtful reactions to blood tests had tests repeated about once a week until negative reactions were obtained. Twelve per cent had positive reactions to serologic tests of the blood and 10 per cent had doubtful reactions. All of the 100 patients had negative reactions to the Wassermann test of the spinal fluid. One spinal fluid contained 17 cells, of which 6 were polymorphonuclear and 11 were lymphocytes. The remainder of the specimens had 10 or less cells. In 3 cases the total protein was 75 mg. per hundred cubic centimeters. In the remainder it was 50 mg. or less per hundred cubic centimeters.

13. Rosenberg, A. A.: Effect of Malaria on Serologic Tests for Syphilis, Bull. U. S. Army M. Dept., January 1945, no. 84, p. 74.

14. Potter, H. W.; Bronstein, L. H., and Gruber, C. M.: Blood and Spinal Fluid Tests for Syphilis in Malarial Patients, J. A. M. A. **127**:699 (March 24) 1945.

Cox and Durant [15] discuss the influence of malaria on flocculation and complement fixation tests for syphilis. Both tests were made on 175 specimens of serum from nonsyphilitic patients with acute malaria and on 140 specimens of serum from nonsyphilitic convalescent malarial patients. Of the 175 specimens followed during the acute phase of malaria, 17 were reported as showing doubtful or positive reactions, whereas a larger number (22 out of 140) of specimens of serum from convalescent patients were reported as giving positive reactions. Neither this study nor any other so far published, however, clarifies the question of false positive reactions to serologic tests in chronic malaria.

Smallpox Vaccination.—A case of smallpox in the Philadelphia area led to the mass vaccination of approximately 1,000,000 persons. Because of this, Favorite [16] had the opportunity to study 202 vaccinated persons, mostly medical students and nurses. In 44 of these there developed a primary cutaneous (nonimmune) reaction at the site of inoculation; in 134 there developed a local accelerated (vaccinoid) form, and 24 were immune. Serologic tests of the blood for syphilis were performed on this group within a reasonably short time prior to vaccination. Of the 202 persons on whom a single blood test was made after vaccination, 19 were found to have positive reactions by one or more serologic technics. These were examined from ten to fifty-seven days following vaccination, but 93.6 per cent of the repeat tests were made before the forty-third day. Twenty-five persons who had negative reactions fourteen days after vaccination were examined fourteen days later, or approximately one month after vaccination. Four of this group were then found to have positive reactions. The incidence of false positive reactions for syphilis following vaccination was 11.8 per cent [sic] regardless of type of vaccination reaction. All the false serologic reactions occurred in the nonimmune and accelerated groups and none in the immune group. All persons with positive reactions to tests were reexamined at regular intervals. At the end of sixty days only 8 had positive reactions, while in eighty days 4 had weakly positive reactions; 2 patients continued to have positive reactions for one hundred days, and the reactions of all became negative within one hundred and twenty days.

Later the entire student body of a medical school was vaccinated against smallpox. Six months later, when a new freshman class had

15. Cox, C. B., and Durant, M. J.: The Influence of Malaria on the Kline and Complement Fixation (Wassermann) Tests for Syphilis, M. J. Australia **1**: 320 (March 31) 1945.

16. Favorite, G. O.: Factors Influencing False Positive Serologic Reactions for Syphilis Due to Smallpox Vaccination (Vaccinia), Am. J. M. Sc. **208**:216 (Aug.) 1944.

enrolled, the entire group was revaccinated, this time not only against smallpox but also against typhoid, paratyphoid and tetanus. This procedure offered an opportunity to determine the role played by the latter type of vaccinations. This study of Favorite's included 323 persons, three fourths of whom had been vaccinated six months previously. Blood tests were made on all prior to revaccination. In 6 subjects a primary cutaneous reaction developed and in 71 an accelerated form; 246 were immune. One month after revaccination, repeated serologic tests for syphilis were performed. Reactions previously seronegative were now positive in 15 persons, among whom 5 had had accelerated and 6 immune vaccinial reactions. Of all these immune subjects, in 2.4 per cent positive serologic reactions developed.

Infections of the Upper Respiratory Tract.—Miscellaneous Immunizations: During the early winter of 1943 there was a moderately severe epidemic of infections of the upper respiratory tract at Fort Jackson, S. C., occurring for the most part in troops who had recently received routine Army immunizations. Loveman[17] reports that when a false positive serologic reaction was suspected in any of these patients, a quantitative serologic test for syphilis was made and repeated as frequently as every week or two until a decision was reached as to biologic false positivity. All were followed for at least one month and often for as long as six months. One hundred soldiers were suspected of having false positive serologic reactions for syphilis. All had at least two initial positive serologic reactions and from two to twenty reactions during their follow-up period. The average time from the first immunization to the appearance of the first positive serologic reaction was thirty-two days. The greatest number of days was one hundred and twenty, and the shortest, five. Ninety-seven per cent stated that they had not had previous penile lesions, and only 4 per cent gave a history of having had gonorrhea. Eighty-six per cent had had both a recent infection in the upper respiratory tract and recent immunizations. Although it was impossible to determine which of these factors was responsible for the false positive serologic reaction, Loveman felt that the latter played a more important role than did the former.

Some supposedly false positive reactions remained for as long as six months. A quantitative test was of definite value in differentiating true from false positive types of reactions. A gradual decrease in titer without specific therapy practically always presaged an eventual negative reaction and thus indicated a false positive reaction.

17. Loveman, A. B.: False Positive Serologic Reactions for Syphilis: Report of One Hundred Cases Following Routine Immunizations and Upper Respiratory Infections, Bull. U. S. Army M. Dept., September, 1944, no. 80, p. 95.

Miscellaneous Conditions.—Rein and Elsberg [18] have studied the serums of persons with the following infections:

1. Vaccinia: Serum was obtained at weekly intervals from 129 patients after smallpox vaccination, in 80 of whom vaccinia developed: 49 had vaccinoid reactions. Of those with vaccinia, 52.2 per cent showed false positive reactions to blood tests; of those with vaccinoid reactions, 34.7 per cent; and of the total, 44.9 per cent. The majority (86.2 per cent) showed the first positive reaction to a blood test between the eighth and the fourteenth day after vaccination, though in some this was delayed to as late as the twenty-first day. Rein and Elsberg were unable to correlate the severity of the response to the vaccination with the height of the quantitatively titered reaction to the serologic test.

In a small series of patients studied serologically after combined typhoid and tetanus immunization the incidence of false positive reactions was insignificant.

2. Infections of the Upper Respiratory Tract: Of 72 patients with primary atypical pneumonia followed for brief periods, many with only one serologic examination, 23.6 per cent had positive serologic reactions. False positive reactions were also observed in 20.2 per cent of 79 patients with miscellaneous infections of the upper respiratory tract.

3. Leprosy: Eighty-five per cent of 80 presumably nonsyphilitic lepers had positive reactions to serologic tests for syphilis.

4. Filariasis: Six (11.3 per cent) of 53 specimens gave doubtful or positive serologic reactions.

5. Leptospirosis: Of single specimens from 87 patients with Weil's disease 43.6 per cent had positive reactions.

6. Malaria: In 44.4 per cent of a small series of nonsyphilitic seronegative inoculated persons false positive reactions developed.

7. Typhus: Single specimens were taken from 104 patients with epidemic and murine typhus, and 39.4 per cent gave positive reactions to serologic tests for syphilis.

The suggested method of study of patients with presumed false positive reactions includes a detailed history, a complete physical examination, a roentgenologic study of the heart and aorta, an examination of the spinal fluid, an examination of contacts and repeated quantitative serologic tests for syphilis for a minimum of three months.

In a later paper, Rein and Elsberg [19] analyze in more detail the

18. Rein, C. R., and Elsberg, E. S.: False Positive Serologic Reactions for Syphilis with Special Reference to Those Due to Smallpox Vaccinations (Vaccinia), Am. J. Syph., Gonor. & Ven. Dis. **29**:303 (May) 1945.

19. Rein, C. R., and Elsberg, E. S.: Studies on the Incidence and Nature of False Positive Serologic Reactions for Syphilis, Am. J. Clin. Path. **14**:461 (Sept.) 1944.

serologic results obtained in the 129 patients vaccinated for smallpox referred to briefly earlier.

Biologic False Positive Reactions to Wassermann Tests of Spinal Fluid.—Scott, Reynolds and Mohr [20] report 7 instances of biologic false positive reactions to Wassermann tests of spinal fluid in seronegative (blood) nonsyphilitic persons during the course of meningitis and 1 instance in which transfer of reagin from blood to spinal fluid may have occurred. The meningitis was tuberculous in 3 patients, meningococcic in 2 and aseptic lymphocytic in 2. In all patients the positive reaction to the Wassermann test of the spinal fluid was confirmed by one or more repeat tests. In all the cases reported the false positive reactions in the spinal fluid were of short duration, but in 1 patient with chronic lymphocytic meningitis the spinal fluid was repeatedly positive during the first forty days of the illness, reverted spontaneously to negative, positive again one hundred and sixteen days after the onset of the disease, at which time the patient suffered a relapse of meningitis, and again reverted spontaneously to negative. Unconfirmed positive reactions to Wassermann tests of the spinal fluid were observed in 1 patient with meningitis due to infection with alpha hemolytic streptococcus, in 2 with meningitis due to infection with Staphylococcus aureus, in 1 with poliomyelitis and in 4 with subarachnoid hemorrhage. The authors conclude that the diagnosis of neurosyphilis based on a positive reaction to a Wassermann test of the spinal fluid alone is unjustified for patients suffering from meningitis and other acute intracranial disorders until repeated examination, performed after these processes have subsided, demonstrate the continued presence of reagin.

VENEREAL DISEASE AND THE WAR

The surrender of the Axis powers and the rapid demobilization of the armed forces abruptly lessen the interest of the general reader in the more purely military aspects of the venereal diseases. Many of the papers which have appeared within the past year are therefore purposely omitted from this review; others are briefly mentioned because of some particular interest.

In the latter category, since it deals with venereal diseases in aviation personnel and is therefore of interest to physicians concerned with civilian as well as with military flying, is the article by Dyar and Scholtz.[21]

20. Scott, V.; Reynolds, F. W., and Mohr, C. F.: Biologic False Positive Spinal Fluid Wassermann Reactions Associated with Meningitis: Report of Eight Cases, Am. J. Syph., Gonor. & Ven. Dis. **28**:431 (July) 1944.

21. Dyar, R., and Scholtz, J. R.: Venereal Disease and Flying Personnel. J. Indiana M. A. **37**:435 (Sept.) 1944.

Physical standards of flying personnel are extremely high, and reactions to drugs may be the cause of accidents; concealed infection and treatment unknown to medical officers take on an added significance when aviators are involved. Expressed in terms of physical and physiologic abilities, the qualities which the flyer must have are a high level of consciousness, alertness, orientation, judgment of time and distance, muscular coordination, short reaction time, visual efficiency, tolerance of altitude and ability to withstand fatigue. Any factor which adversely affects these qualities impairs the ability of the individual to perform flying duty. Venereal diseases must be considered from three standpoints as they affect flying performance—namely, the possible effects of the disease on normal physiology and on the occurrence of disturbances characteristic of flight and the possible accentuation of minor pathologic changes, ordinarily below the clinical horizon, under flying conditions.

Lymphogranuloma venereum and granuloma inguinale are disqualifying for any type of military service. These diseases are chronic; no satisfactory treatment is available, and they represent a medical burden even though in most instances they do not result in serious physical disability. Persons having uncomplicated infections with Ducrey's bacillus are acceptable for general military service, since the great majority of them readily respond to sulfonamide drugs and are cured within a few weeks. Such persons are then perfectly able to carry on any type of military duty, including flying, if otherwise qualified.

Persons infected with uncomplicated gonorrhea are also acceptable for general military service, since it, too, can in most instances be rapidly cured, after which the patient is physically qualified for any type of military duty. If he is receiving sulfonamide drugs, the patient is temporarily disqualified for flying. The availability of penicillin reduces the period of disability from gonorrhea almost to the vanishing point, since a curative dose can be administered in less than twelve hours and there are no reactions to the drug which prevent immediate return to flying duty.

The presence of syphilis of the central nervous or cardiovascular systems, or of the viscera or, in fact, any clinically active syphilis—other than primary and secondary—is disqualifying for flying duty in the Army. On the other hand, persons with primary, secondary or latent syphilis, regardless of the amount of treatment, are so qualified when not actually under treatment.

Most of the discussion by Dyar and Scholtz of drugs for flying personnel is outmoded by the advent of penicillin, which has almost completely changed the perspective in regard to both gonorrhea and syphilis. This drug is so completely free of untoward reactions that

flying personnel may return to flying duty immediately on completion of treatment.

There are no verified reports of air accidents which can be attributed to the effects of venereal diseases or of the drugs used in their treatment. Several such reports have been investigated, and in no instance has the disease or the drug been proved to have been the proximate cause of the accident. However, the nature of air accidents is such that it is usually impossible to determine what role, if any, medical factors play.

Dyar [22] says that education, an important factor in the control of venereal diseases in civilian life, is the most significant part of the program in the Army. In civil communities sound efforts toward control are based primarily on epidemiology, and the responsibility for control of the sources of venereal disease infection is shared jointly by civil health agencies and law enforcement agencies. The importance of education concerning venereal disease is officially recognized in the United States Army by regulation and directive. The fact that most of the current infections occur in personnel who are ignorant of the facts regarding venereal disease indicates either that there has been a failure to appreciate the importance of education, or that there has been neglect of utilizing available technics and of developing new procedures.

Dyar emphasizes that education concerning venereal disease must be specially adapted to varying personnel; a few scientifically accurate facts must be presented with a fully defined purpose, and the presentation must be well organized, coordinated, progressive and repetitive, but at the same time simple, brief and attractive.

In a paper read before the National Venereal Disease Control Conference, Padget [23] says:

> The venereal diseases will be, as they have always been, a world problem, and with the conditions which we may anticipate to obtain in a postwar world, with tremendous shiftings of large population groups and with travel between and intercourse among the various peoples of the world on a scale so far unprecedented, we may take for granted that the venereal disease problem will be international, and we in the United States may base our plans upon that concept. . . . Among the large body of men who eventually will return to the United States from Europe there will be a number who have acquired a venereal disease. This fact and its possible significance to the public health of the United States must be carefully considered. . . .
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> The venereal disease control program in the European Theater of Operations . . . got under way in the summer of 1942, and became a full-time venture in September

22. Dyar, R.: The Medical Officer and the Venereal Disease Education of the Soldier, Ven. Dis. Inform. **26**:27 (Feb.) 1945.

23. Padget, P.: U. S. Army Experiences in Venereal Disease Control in the European Theater of Operations, Am. J. Syph., Gonor. & Ven. Dis. **29**:352 (May) 1945.

of that year. . . . From the beginning it was apparent that whereas any venereal disease control program is made up of the same five or six basic ingredients, the technique of application of these various elements must be adjusted to meet local conditions. . . .

Basically, a venereal disease control program deals with four elements: the susceptible population—in our special case the soldier in the United States Army; the infected population—made up of the group of promiscuous women, an unknown number of whom are infectious at a given moment; the number of sexual contacts which take place between the susceptible group and the potentially infectious; and protective measures taken to reduce the risk of infection when exposure has occurred. . . .

As we review these various avenues of approach, examination of what is meant by education will suffice to illustrate the necessity for developing a venereal disease control program with consideration of local problems. All too frequently we encounter the use of the term "education" without the slightest consideration of what it is that should be taught. Certainly the soldier should know the fundamentals of human anatomy, sex hygiene and the nature of the venereal diseases. . . .

Our experiences with prophylaxis are most interesting. There was, of course, a considerable variation in education and training of the soldiers reaching us, depending on how long they had been in the Army before being shipped overseas. . . . In the United Kingdom, however, our soldiers encountered relatively few professional prostitutes. . . . The vast majority of the sexual intercourse which took place was on a friendly and noncommercial basis. This had the immediate and readily discernible effect of markedly reducing the impetus to seek station prophylaxis. . . . By contrast condoms were extensively used and chemical pocket prophylactic kits were not infrequently employed.

The situation in France has been entirely different. The soldiers are all aware that professional prostitution flourishes and up to the present there has been a much more extensive use of station prophylaxis than was the case in the United Kingdom. . . .

Surveying the situation, it became apparent that a contact investigation scheme was essential as a venereal disease control measure among our troops. The enactment of the British Defense Regulation 33B made it possible for us to obtain and transmit the necessary information concerning sex contacts, and the Chief Medical Officer of the Ministry of Health, Sir Wilson Jameson, gave our tentative plan enthusiastic approval and paved the way for arrangement with local Medical Officers of Health in the areas in which we had troops stationed. Eight U. S. Army nurses (regular members of the Army Nurse Corps) were selected as the field workers for the scheme by virtue of previous training and experience in public health nursing. . . . They interviewed soldiers with venereal disease, got from them as much as could be obtained regarding the identity of their sexual contact or contacts, identified such of these women as was possible and presented them with a tactfully worded invitation to avail themselves of the services of the nearest clinic of the local health authority. . . .

In the summer of 1942, when our first troop concentration in the United Kingdom began, the venereal disease rate among our troops in the United Kingdom was essentially the same as that obtained for troops in training in the United States. During the autumn and particularly in the general slump which followed the setting off of the African expedition, the venereal disease rates rose to reach a peak just after the turn of the year, at which time the rate was conspicuously higher than that obtained in the United States. Since that time, however, the rate has pro-

gressively declined, at first rapidly, in the first six months of 1944 more slowly, but the downward trend up until D Day was consistent and sustained, to compare favorably . . . with rates for the troops remaining in the United States.

In England, we had been the guests of people who spoke a similar and frequently understandable language and from whom we differed in morals and social customs only in details. In France, we encountered an equally friendly nation—a nation in fact more given to being demonstrative about friendship than are the British—but with a language which is strange to most of our soldiers, and manners and social customs which differ sometimes widely from our own. The differences are so great that in developing a venereal disease control program applicable to our troops in France, very little of our British experience could be employed . . . All over France there are licensed brothels. Streetwalkers are also licensed. . . .

During the occupation in all communities in which we had troops garrisoned, the enemy had taken over one or more of the local brothels and had operated them exclusively for the Wehrmacht. Among captured enemy documents, we found what would be called in our Army an SOP (i. e., Standard Operating Procedure) for the creation and operation of brothels. This 17-page mimeographed circular is a masterpiece of completeness. . . . There was an elaborate procedure for gaining entrance. . . . In spite of this complicated ritual, the enemy had a disastrous time with venereal infections in his French garrison and in two areas in which we have captured complete records of the experience, the venereal disease rates were over 125 per 1000 per year. . . .

To complete the contrast is the situation with regard to the practicability of epidemiologic investigation. In the British experience . . . we could get information worth following for epidemiologic study. . . . In France, however, only a negligible number of our soldiers who acquire a venereal disease are able to give useful information regarding the identity of their contact. . . .

Schwartz [24] presents a current appraisal of the venereal disease situation in the United States Navy and suggests the trend of the future. Although the venereal disease rate for the entire Navy has fallen off sharply during recent years, and is now at the lowest point in the history of the Navy, roughly 25 new admissions per thousand men per year, the rate in the forces in the continental United States has been climbing steadily and at an increasing speed since 1942. The rate for 1943 was 9 per cent above that for 1942, and for the first six months of 1944, 11 per cent above that for 1943. The author points out that the general downward direction of the entire rate for the Navy reflects the very low rate now being experienced among substantial elements of the naval forces overseas and that this is a condition which normally accompanies intense combat activity. As combat activity decreases, a situation analogous to the experience after Armistice Day of World War I may well develop. At that time the rate increased within one year by 60 per cent. The author warns against complacency and reiterates the

24. Schwartz, W. H.: Venereal Disease Control in the Navy: A Current Appraisal with a Comparative Look at History and the Future, J. Social Hyg. **31**:34 (Jan.) 1945.

need for an intensified and expanded program for the control of venereal disease.

The author of a special article [25] finds that the average length of hospitalization for Army patients with venereal disease in 1939 was forty-two days. By 1944 this figure had declined to six and one-half days. Even in the face of a rise in admission rate, a saving in man power has been accomplished. The replacement of local therapy by sulfonamide drugs and of the latter by penicillin has effected as of September 1944 a tremendous decrease in the duration and complications of gonorrhea. For syphilis, the introduction in July 1942 of a twenty-six week plan of oxophenarsine hydrochloride–bismuth therapy effected a substantial saving in length of treatment. As of October 1944, War Department Technical Bulletin, TB Med. 106, "Penicillin Treatment of Syphilis,[26] introduced the treatment of syphilis with penicillin on an Army-wide basis. With a total dosage of 2,400,000 units given in sixty consecutive intramuscular injections at three hour intervals, day and night, the total treatment time for syphilis was reduced to seven and one-half days. This method is said to be at least as effective as any plan of treatment heretofore employed and much less dangerous.

Hinrichsen [27] discusses at length and in detail venereal disease in the major armies and navies of the world. Little actual statistical information was available before the nineteenth century. The articles does not lend itself to adequate abstraction, and the interested reader is referred to the original.

Civilian Aspects.—The author [28] of an editorial expresses doubt that, despite the promise of the new chemotherapeutic agents effective against syphilis and gonorrhea, the eradication or even the control of venereal disease is possible in the immediate future. Although the present low rate of these diseases in the armed forces is commendable, it is pointed out that it was not until after the last Great War that the incidence of syphilis and gonorrhea reached its peak. The recent advances in therapy, although highly effective, have introduced new problems for the health administrator—e. g., asymptomatic carriers of gonococci and an increased susceptibility to reinfection of patients with early syphilis

25. Improvements in Treatment of Venereal Disease, Bull. U. S. Army M. Dept., June 1945, no. 89, p. 76.

26. Penicillin Treatment of Syphilis, United States War Department, Technical Bulletin (TB Med 106), Washington, D. C., Government Printing Office, October 1944.

27. Hinrichsen, J.: Venereal Disease in the Major Armies and Navies of the World, Am. J. Syph., Gonor. & Ven. Dis. **29**:80 (Jan.) 1945.

28. Shall We Control Venereal Disease? editorial, Am. J. Pub. Health **34**: 1185 (Nov.) 1944.

treated by intensive methods. The need for more vigorous epidemiologic control is stressed.

Case Finding.—Heller [29] discusses future aspects of venereal disease control. He estimates that of about 230,000 new cases of syphilis contracted in this country annually, only about three fourths are discovered and treated and that less than one half of the patients found remain under treatment long enough to insure against infectious relapse. The unfound and untreated one fourth and the insufficiently treated lapsed cases are the source of infection for the annually recurring new crop of early syphilis, and they accumulate year in and year out to form the great reservoir of late and latent syphilis. No matter how effective new procedures of treatment may be, they can have little value for reduction of the rate of attack unless persons who are infectious are brought to the physician before they have spread their infections to others.

In the past, the English have not utilized the important case-finding and control measure—investigation of contacts—because the authorities considered this method to be an infringement of individual rights. Following the successful demonstration by a small team of United States Army Public Health Nurses in tracing the female contacts of personnel of the American armed forces in England, there has been in that country an awakening of interest in the investigation of contacts. Evidence of this is indicated by a series of articles [30] in the *British Journal of Venereal Diseases*. A pilot study instituted in Tyneside, a report of which is included in one of the papers, proved highly successful. The favorable comment evoked by the results of this experiment suggests a wide application of investigation of contacts in England in the future.

Sternberg and Larimore [31] believe that the postwar period will present far greater assets for the control of the venereal diseases than have been available at any previous time. A large number of physicians and lay personnel trained by the Army and experienced in the principles

29. Heller, J. R.: Venereal Disease Control of Tomorrow, J. Social Hyg. **31**:16 (Jan.) 1945.

30. (*a*) Manchee, D. M.: The Social Aspect of the Venereal Diseases: I. The Work of the Almoner, Brit. J. Ven. Dis. **21**:12 (March) 1945. (*b*) Walies, M. A.: The Social Aspect of the Venereal Diseases: II. Contact Tracing and the Prostitute, ibid. **21**:15 (March) 1945. (*c*) Johns, H. M.: The Social Aspect of the Venereal Diseases: III. Contact Tracing, ibid. **21**:17 (March) 1945; (*d*) The Social Background of Venereal Disease: A Report on an Experiment in Contact Tracing and the Prostitute and an Investigation into Social Conditions; Tyneside Experimental Scheme in Venereal Disease Control, October 1943 to March 1944, ibid. **21**:26 (March) 1945. (*e*) The Venereal Disease Contact, editorial, ibid. **21**:1 (March) 1945.

31. Sternberg, T. H., and Larimore, J. W.: Army Contributions to Postwar Venereal Disease Control Planning, J. A. M. A. **127**:209 (Jan. 27) 1945.

of venereal disease control will be available. The postwar population will be diluted by 9,000,000 soldiers, and thus the general educational level concerning venereal diseases will be raised to a new high; it seems certain that future programs for the control of venereal diseases will be accorded increased public support. Efforts to reimpose a black-out on the venereal diseases are doomed to failure. Remarkable advances in treatment climaxed by the introduction of penicillin will add great impetus toward achieving the goal of universal case finding and case holding. These factors, added to the stabilization of community life and the return of an opportunity to follow the natural instincts of monogamous relationships, all lead to the conclusion that there will be an unprecedented opportunity to reduce the incidence of the venereal diseases to a manageable minimum.

Ingraham and Greenbaum [32] point out a fundamental fact too often entirely ignored by venereal disease bureaus in health departments. The management of gonorrhea and syphilis in clinics reaches only a small portion of the persons infected. As the magnitude of the case-finding problem is more clearly defined and as the vast amount of hidden venereal disease, unknown to any source of treatment, becomes evident, the necessity of actively enlisting the support of the private physician becomes apparent. The Philadelphia Department of Public Health has utilized professional and lay education and adopted consultation and laboratory services together with distribution of free drugs. The interesting and unique factor in the Philadelphia program, however, is the active solicitation of the private physician by the health department, so as to integrate all available medical facilities toward the same end. It was found completely unsatisfactory merely to tell the prospective patient to consult his family physician. A direct appeal was made by a letter jointly sponsored by the County Medical Society and the Department of Public Health. Approximately two thousand, five hundred physicians responded, and three fourths of those who treated gonorrhea or syphilis (one thousand, one hundred and sixty-four physicians in all) agreed to have their names published for purposes of facilitating a proper patient referral mechanism in the community. A survey conducted to ascertain the effectiveness of this effort showed a definite increase in the number of patients with venereal disease receiving private medical care in Philadelphia. The prevalence of treatment for syphilis by private physicians has increased 86 per cent since 1940, and for gonorrhea 30 per cent in the same period.

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32. Ingraham, N. R., Jr., and Greenbaum, S. S.: Public Health Venereal Disease Control: The Private Physician's Increasing Responsibility; a Report of the Success of Philadelphia's Cooperative Plan, J. A. M. A. **125**:527 (June 24) 1944.

DRUGS

Although the advent of penicillin in the treatment of syphilis has lessened interest in the toxic drugs arsenic and bismuth, there is, nevertheless, a strong possibility that both of the latter will continue to be of value for some years to come. It may be desirable to employ one or both of them simultaneously with penicillin or to use them alone, without penicillin, for certain special purposes. For these reasons it is still justifiable to devote considerable space to articles dealing with recent results obtained with these metals.

Oxophenarsine Hydrochloride.—Since it is frequently necessary to administer treatment for syphilis and gonorrhea simultaneously, Cranston, Clark and Strakosch [33] have studied the acute toxicity for mice of oxophenarsine hydrochloride and sodium sulfathiazole, given separately and together, in order to determine whether these drugs are synergistic, additive, antagonistic or without effect on one another as regards toxicity. By use of large numbers of mice and by administration of the drugs intraperitoneally, it was found that the combined toxicity was greater than that of either drug alone, as the LD_{50} dose of the combination was 65 per cent of the LD_{50} dose of each drug alone. The results indicated that the toxic effects are additive but less than algebraic summation.

Since the therapeutic efficacy of oxophenarsine hydrochloride in the treatment of experimental syphilis in rabbits is increased approximately fourfold when the drug is administered concurrently with physically induced fever while the toxicity is only doubled, Stokinger, Dorn, Boak and Carpenter [34] have studied the arsenic content of rabbit tissues following treatment with oxophenarsine hydrochloride and fever and with oxophenarsine hydrochloride alone, in an effort to determine whether a relationship exists between the distribution of arsenic and the increased therapeutic efficacy and toxicity. Significantly higher concentrations of arsenic were observed in the tissues of rabbits treated with oxophenarsine hydrochloride plus fever than in those treated with the drug alone. It was found that the elimination of arsenic was retarded in the fever-treated animals and that the greatest increase in arsenic content occurred in the liver and kidneys.

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33. Cranston, E. M.; Clark, W. G., and Strakosch, E. A.: The Acute Toxicity for Mice of "Mapharsen" and Sodium Sulfathiazole Administered Separately and in Combination, J. Pharmacol. & Exper. Therap. **81**:284 (July) 1944.

34. Stokinger, H. E.; Dorn, F. L.; Boak, R. A., and Carpenter, C. M.: The Effect of Fever on the Distribution of Arsenic in the Tissues of Rabbits Injected Intravenously with Mapharsen, Am. J. Syph., Gonor. & Ven. Dis. **28**:465 (July) 1944.

New Phenylarsenoxides.—Continued efforts are being made to discover new arsenicals which have both a higher therapeutic index and lower toxicity. Eagle and his co-workers [35] have studied 13 amide-substituted phenylarsenoxides (-$RCONH_2$, -RSO_2NH_2) and found that they were, per unit of arsenic, only 4.5 to 13.5 per cent as toxic as the parent phenylarsenoxide. The treponemicidal activity in vitro was not reduced to the same degree; therefore the ratio of treponemicidal activity to toxicity was 1.9 to 6.1 times more favorable than that of phenylarsenoxide. The favorable effect of amide groups was confirmed for ten of these compounds by assays of toxicity and therapeutic activity in syphilitic rabbits. The regularity with which substituents containing terminal amide groups decreased the toxicity and increased the chemotherapeutic index of phenylarsenoxide suggests that some members of this series may be of clinical utility.

Local Prophylaxis of Syphilis with Arsphenamine.—Eagle and his co-workers [36] have studied local chemical prophylaxis with phenylarsenoxides in experimental syphilis. They summarize as follows:

1. Nine trivalent arsenicals [all phenylarsenoxides] . . . have been studied with respect to prophylactic activity in rabbit syphilis. One-half c.c. of solutions in propylene glycol was rubbed for four minutes over a superficial skin incision, at varying intervals before and after its inoculation with a suspension of T. pallidum (Nichols' strain) containing 10^7 organisms per c.c.

2. All the compounds were found to be effective, and approximately in proportion to their direct treponemicidal activity. The concentration necessary to protect half the animals when applied four hours after inoculation varied from 0.06 to 0.15 per cent in the case of the more active compounds, to 1.5 per cent in the case of the least active compound.

3. The effective concentration of the p-$CONH_2$ phenyl arsenoxide varied with the time interval between inoculation and application. A 1:2,000 solution protected half the animals when applied five minutes after exposure; it required a 1:500 concentration to protect half the animals four hours after exposure; and only concentrations in excess of 1:100 had a similar effect 22 hours after exposure. The prophylactic efficacy of this compound, although definite, was somewhat less pronounced when it was applied before inoculation. The concentrations which protected 50 per cent of the animals when applied 5 minutes, 4 hours and 22 hours before inoculation were respectively, 1:2,000, 1:200-1:500, and 1:50.

4. The effect of the p-$CONH_2$ compound, and presumably, of the other arsenoxides here tested, was due to a direct treponemicidal action on the organisms in the skin itself, and not to a systemic effect on an established infection.

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35. Eagle, H.; Hogan, R. B.; Doak, G. O., and Steinman, H. G.: The Toxicity and Treponemicidal Activity of Amide-Substituted Phenyl Arsenoxides and Their Derivatives, J. Pharmacol. & Exper. Therap. **81**:142 (June) 1944.

36. Eagle, H.; Hogan, R. B., and Fleischman, R.: The Local Chemical Prophylaxis of Experimental Syphilis with Phenyl Arsenoxides, Am. J. Syph., Gonor. & Ven. Dis. **28**:661 (Nov.) 1944.

(a) As shown by urinary and fecal excretion, of the 0.5 mg. which was regularly protective on local application 1 hour after inoculation, less than 10 per cent was absorbed through the skin. In rabbits averaging 2.5 kg., it required more than fifty times that amount of mapharsen injected intravenously to abort syphilitic infection when the animals were inoculated intratesticularly 1 hour previously with only 1,000 organisms.

(b) Even 100 times the concentration which was effective when applied over the inoculated area was ineffective when applied over a similar incision on the opposite side of the back, or 1 to 2 inches from the inoculated area.

5. It follows that, when a heavy suspension of T. pallidum is rubbed into an open cut in the rabbit skin, the organisms remain in the skin or adjacent soft tissues, susceptible to the local treponemicidal action of prophylactic agents, for as long as 8 to 22 hours.

6. The concentrations of arsenical effective for periods of four to eight hours after inoculation caused only slight reaction on intracutaneous injection.

7. The stability of the selected compounds here discussed, the time interval over which they remain effective, the low concentrations necessary within reasonable time periods, and the absence of local irritative effects at those concentrations, all offer promise that some of these compounds may be of value in the prophylaxis of the human disease.

Bismuth.—Kendell and his co-workers [37] present figures to demonstrate that after 2 cc. of oil-insoluble bismuth (150 mg. of elemental bismuth) administered sixteen hours before fever-chemotherapy treatment, the daily urinary excretion of bismuth during the first six days after treatment remains consistently lower than 2 mg. of elemental bismuth, the "therapeutic bismuth level." It was therefore decided to administer concomitant water-soluble bismuth (sodium bismuth thioglycollate) to a series of 69 patients. From the data presented it is evident that the addition of water-soluble bismuth to the described method of fever plus chemotherapy will raise the urinary excretion of bismuth to "the therapeutic level." However, the amount needed to attain this level cannot be given without potentially serious reactions. Of the 69 patients who received water-soluble bismuth in addition to oil-soluble bismuth, 10 had significant complications, and of these 3 were critically ill. There was 1 death from acute nephrosis and ulcerative stomatitis. During the period in which these 69 patients were studied, 173 other patients were given the same routine except for the water-soluble bismuth. Of these, 3 had complications and none was seriously ill. The complications in both series occurred during the postfever period and were classified as acute nephrosis, acute hepatitis, or azotemia and/or ulcerative stomatitis. The authors do not provide further clinical details concerning reactions to treatment.

37. Kendell, H. W.; Craig, R. M.; Schwemlein, G. X., and Aron, H. C. S.: Artificial Fever-Chemotherapy: I. Bismuth Excretion Studies, Arch. Phys. Therapy **25**:593 (Oct.) 1944.

REACTIONS TO TREATMENT

Hepatitis.—The epidemic of jaundice in England during or after the administration of organic arsenicals has recently been shown to be infectious hepatitis of virus causation transmitted from patient to patient by technical error.[38] This fact renders of secondary importance the papers of Peters and his associates[39] and Beattie and Marshall.[40] Before the demonstration of the virus origin of this epidemic of jaundice these investigators were engaged in a study of dietary deficiency as an etiologic factor and of certain forms of dietary treatment. Peters and his group studied the prophylactic and curative effect (on jaundice) of cysteine, casein and methionine but without dramatically conclusive results. Beattie and Marshall attempted to demonstrate that jaundice could be prevented by the administration of sulfur-containing amino acids (casein digest, cysteine, methionine) during antisyphilitic treatment, but again without definite results.

Glynn and Himsworth[41] describe a method for producing necrosis of the liver in rats by means of a protein-deficient diet. This necrosis has the clinical and pathologic features of massive acute necrosis of the liver. It closely resembles acute yellow atrophy in human patients and progresses to a condition of scarring similar to that of nodular hyperplasia. The onset of this acute necrosis is delayed thirty to one hundred days after institution of the experimental diet. The necrotic process does not uniformly involve the liver; areas of total necrosis alternate with areas where the liver cells are apparently healthy. The delay in onset and the haphazard distribution of lesions differentiate this nutritional necrosis of the liver from the immediate acute uniform zonal necrosis caused by many liver poisons (e. g., chloroform, carbon tetrachloride). This nutritional necrosis was found to be due to lack of casein in the diet, and the exhibition of methionine in a dose of 20 mg. per rat per day was completely protective.

Drill and Loomis[42] report abnormal hepatic function in dogs as measured by excretion of sulfobromophthalein sodium after single injec-

38. Mohr, C. F.; Scott, V.; Hahn, R. D.; Clark, E. G.; Moore, J. E., and Sheehan, H. L.: Epidemiology of Infective Hepatitis, Lancet **2**:8 (July 1) 1944.

39. Peters, R. A.; Thompson, R. H. S.; King, A. J.: Williams, D. I., and Nicoli, C. S., with a statistical appendix by Greenwood, M., and Martin, W. J.: The Treatment of Post-Arsphenamine Jaundice with Sulphur-Containing Amino-Acids, Quart. J. Med. **14**:35 (Jan.) 1945.

40. Beattie, J., and Marshall, J.: Studies on Hepatic Dysfunction: II. The Value of Sulphur-Containing Amino-Acids and Casein Digest in the Prevention of Post-Arsphenamine Jaundice, Brit. M. J. **2**:651 (Nov. 18) 1944.

41. Glynn, L. E., and Himsworth, H. P.: Massive Acute Necrosis of the Liver: Its Significance and Experimental Production, J. Path. & Bact. **56**:297 (July) 1944.

42. Drill, V. A., and Loomis, T. A.: Effect of Mapharsen on Bromsulphalein Retention in Normal Dogs, Proc. Soc. Exper. Biol. & Med. **58**:296 (April) 1945.

tions of oxophenarsine hydrochloride in large doses. Retention of sulfobromophthalein sodium was observed in 59 per cent of 17 normal dogs after a single injection of 60 mg. of this drug. Retention of dye occurred irrespective of dosage over a range of 2.7 to 9.1 mg. per kilogram. Animals showing retention of dye from the initial injection of oxophenarsine hydrochloride showed either less retention or a complete return to normal after subsequent injections. Dogs which initially showed a normal retention of dye also had normal retention following two subsequent injections.

In an attempt to determine whether the administration of bismuth interferes with recovery from hepatitis occurring during the course of arsenical therapy, Forbes [43] followed the hippuric acid excretion test on two groups of patients, one group receiving bismuth during the period of jaundice and the other receiving no form of antisyphilitic treatment. All patients had early syphilis and, except for the bismuth, received identical supportive treatment. In the 10 patients who received bismuth during the course of their illness, the recovery periods varied from 14 to 44 days (mean, 28.5 days). The recovery periods of 11 patients who received no bismuth varied from 19 to 48 days, with a mean of 34.4 days. Thus, in these small groups, the bismuth-treated patients recovered slightly more rapidly than those not receiving bismuth, but the difference is not considered to be statistically significant. Certainly the administration of bismuth did not retard recovery of hepatic function in these patients.

Nephrosis.—Heyman [44] says that the widespread use of bismuth in syphilotherapy and the paucity of reports of its toxic manifestations are evidence that bismuth therapy is relatively safe. It must not be assumed, however, that the use of bismuth is totally without danger, for there are recurring reports of deaths following its injection. Most of these fatalities are caused by the toxic effects of bismuth on the liver or kidney. Although such serious systemic reactions are uncommon, 4 patients with severe visceral manifestations of bismuth poisoning have been seen at Grady Hospital within the past few years. The most constant feature of their cases was the production of varying degrees of renal insufficiency following the administration of bismuth. This was manifested as anuria, azotemia, albuminuria and decreased excretion of phenol sulfonphthalein.

Although the nephrotoxic action of bismuth is known, its occurrence in some patients and not in others has not been fully explained. In

43. Forbes, J. R.: Bismuth Therapy in Jaundice During Antisyphilitic Treatment, Brit. M. J. **2**:852 (Dec. 30) 1944.

44. Heyman, A.: Systemic Manifestations of Bismuth Toxicity: Observations on Four Patients with Pre-Existent Kidney Disease, Am. J. Syph., Gonor. & Ven. Dis. **28**:721 (Nov.) 1944.

many cases renal complications occur in supposedly healthy adults after one or several injections of the drug. That preexistent renal damage may be a predisposing factor in bismuth poisoning has been repeatedly discussed in the literature. The prevalent impression among syphilologists is that with the usual doses employed the drug causes so few renal complications that it can be used for patients with previous renal disease. Although this may be generally true, there have been so many reports that such patients exhibit an intolerance to bismuth that further observation is warranted.

Treatment of Severe Arsenical Reactions.—To date, little has been published regarding the antiarsenical activity of BAL, a drug whose composition has not yet been made public, in the interests of national security. Certainly this drug holds promise in the treatment of the more serious arsenical reactions. The author of an article [45] in the *Bulletin of the United States Army Medical Department* says that BAL is a specific antidote for systemic arsenic poisoning. Once the diagnosis of arsenic poisoning has been made, BAL should be administered whether the poisoning is in an early or an advanced stage. An immediate intramuscular injection of 10 per cent BAL in oil should be given deep into the muscles of the buttocks. Dosage must be adjusted to body weight: 125 pounds (56.7 Kg.), 2.5 cc.; 150 pounds (68 Kg.), 3 cc.; 175 pounds (79.4 Kg.), 3.5 cc., and 200 pounds (90.7 Kg.), 4 cc. The injection should be repeated every four hours to a total of four doses. In cases of severe poisoning the interval between the first and second dose should be shortened to two hours and the course of therapy extended to include single daily half-doses for three or four days. BAL in oil causes certain reactions. These may include constriction in the throat, oppression in the chest, burning of the lips, reddening and lacrimation of the eyes, dryness of the mouth, nervousness and restlessness, nausea and vomiting and local tenderness. There may be a transient rise in blood pressure. These reactions do not as a rule contraindicate the continued administration of the full course of four injections of the drug.

Intensive Treatment of Early Syphilis.—In the course of a general review of chemotherapy Dale [46] remarks, in referring to the arsenical chemotherapy of syphilis:

> And there comes thus to our notice another factor in an effective chemotherapeutic action, which has not always, I suspect, received sufficient attention—namely, the need for a sufficiently prolonged and continuous action. This need is almost implied in the conception of the process as essentially an arrest of the multiplication of the parasites rather than an immediately lethal action on them.

45. Acute Arsenic Poisoning, Bull. U. S. Army M. Dept., May 1945, no. 88, p. 13.

46. Dale, H.: A Prospect in Therapeutics, Brit. M. J. **2**:411 (Oct. 2) 1943.

What is required is not the sudden attainment of a concentration sufficient to kill most of the parasites, at the risk of a concomitant injury to the host's tissues, but the long-continued maintenance of a much lower and safer concentration, just sufficient to suppress the propagation of the parasites, without harming the cells of the host.

The importance of these sentences to investigators in the field of intensive arsenotherapy of syphilis and of penicillin treatment as well (to be discussed later) cannot be too strongly emphasized.

Neilson and his co-workers [47] treated 487 patients with early syphilis intensively for an average of five days, utilizing the continuous intravenous drip. Each patient received from 900 to 1,200 mg. of oxophenarsine hydrochloride. A second course was given to 15 patients. It was necessary to discontinue treatment in 23 patients because of severe toxic reactions. There were three separate treatment groups. The first received oxophenarsine hydrochloride alone; the second received, in addition, a single intramuscular injection of 5 cc. of 10 per cent bismuth subsalicylate in oil, and the third, six weekly injections of 150 mg. of bismuth in a follow-up clinic, in addition to the 5 cc. given in the hospital. There were 4 deaths from treatment among patients in whom intensive therapy was initiated, a fatality rate of 0.79 per cent. In 23 additional patients severe reactions were experienced that might have resulted in death if treatment had not been discontinued. Nonfatal reactions were frequent.

Results of treatment are reported for only 155 patients, since this was the total number followed for five months or longer. Of these, the reactions of 68.3 per cent had become seronegative; those of 10.3 per cent were almost seronegative; those of 3.2 per cent were still seropositive; 15 per cent had suffered serologic or mucocutaneous relapse, and 3.2 per cent had a presumed reinfection or superinfection.

Berry and Mitchell [48] report a follow-up study of the cases of 50 of 100 patients with early syphilis treated by the five day massive dose method. Twenty-three patients were followed for one to two years, 12 from two to three years, and 11 patients were followed over three years. The duration of follow-up of the remaining 4 patients is not stated. For only 4 is treatment classified as failure. Among the 100 patients treated there was 1 fatality due to hemorrhagic encephalitis. The only other serious complication was 1 case of toxic hepatitis and polyneuritis.

47. Neilson, A. W.; Blaney, L. F.; Stephens, L. J., and Maxwell, R. W.: Intensive Chemotherapy of Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **28**:553 (Sept.) 1944.

48. Berry, N. E., and Mitchell, L. I.: Four Years' Experience in Massive Dose Therapy of Early Syphilis, Canad. M. A. J. **51**:356 (Oct.) 1944.

Cannon and his co-workers [49] report the results of treating 332 patients with early syphilis with massive doses of arsphenamine by the syringe method. Treatment was carried out in the hospital over a period of five to six days. The drug was given in 2 per cent solution by the syringe method three or four times daily. The total dose ranged from 1.5 Gm. in the beginning of the experiment to a maximum of 4.4 Gm. Of the 332 patients treated, 178 have been followed from six months to three years. One hundred and eighteen patients (66 per cent) are clinically and serologically negative and have normal spinal fluids. Fifty-seven patients had an unsatisfactory outcome. Of these, 36 had cutaneous relapses. Of all the 178 patients only 27 failed to become serologically negative at some time during the period of observation. Of all the patients treated 12 had severe reactions. Two had encephalitis and recovered; 3 had hepatitis, and of these 1 died; 2 had exfoliative dermatitis; 3 had persistent neuritis, and 2 had blood dyscrasias. As a result of their experience, the authors conclude that the treatment of early syphilis with arsphenamine by the multiple syringe method over a period of five or six days is ineffective, dangerous, expensive and altogether impractical.

An account of the results of intensive arsenotherapy for early syphilis in the United States Army in the European Theater of Operations is presented by Pillsbury and his associates.[50] Intensive arsenotherapy was undertaken in April 1943 because of the difficulties of carrying out standard prolonged treatment for early syphilis under conditions of global warfare and because these difficulties caused serious interruptions in treatment which greatly reduced its effectiveness. The scheme of treatment consisted in the administration of a total of 20 mg. of oxophenarsine hydrochloride per kilogram of weight, given in twenty equal injections by the syringe technic over a twenty day period, plus eight injections of bismuth subsalicylate during the same time interval. In a series of 775 consecutive patients, treatment was completed for 96.3 per cent with no deaths. Data as to the result of treatment were incomplete, since only 435 patients had been followed for a minimum of four months. The authors have the impression, however, that the ultimate results will compare favorably with those obtained by prolonged methods of treatment.

Marin and Lambert [51] treated 62 patients with early syphilis by daily injections of 0.06 Gm. of oxophenarsine hydrochloride for thirty days.

49. Cannon, A. B.; Fisher, J. K.; Rodriguez, J. J.; Beattie, G. F., and Maechling, E.: Intensive Arsenotherapy, J. A. M. A. **126**:544 (Oct. 28) 1944.

50. Pillsbury, D. M.; Courville, C. J.; Crede, R. H.; Myers, J. E., and Wise, C. R.: The Intensive Therapy of Early Syphilis, Brit. J. Ven. Dis. **20**:154 (Dec.) 1944.

51. Marin, A., and Lambert, A.: A Thirty Days' Treatment of Early Syphilis (Preliminary Report), Canad. M. A. J. **51**:265 (Sept.) 1944.

Three months after cessation of treatment, 51 per cent were seronegative. Of 27 patients followed twenty to twenty-eight months only, 43 per cent were seronegative. Of 17 patients whose spinal fluids were examined, all were seronegative. Erythema of the ninth day was noted four times, icterus was noted once, and menace [sic] of malignant granulopenia was noted thirteen times.

Goldblatt [52] treated 104 men and 3 women with a total dose of 1,800 mg. of oxophenarsine hydrochloride. The drug was administered intravenously in daily doses of 60 mg. for thirty consecutive days. Of the entire group 27 had primary syphilis; 21, secondary syphilis; 17, late syphilis, and 7, congenital syphilis; in 35 the disease was latent. There were no fatalities, nor were any serious reactions encountered. Two patients had an erythema of the ninth day; neither was seriously ill. Twelve patients with primary syphilis were seronegative and remained so for the follow-up period. Eighty-one per cent of the group had positive serologic reactions for syphilis at the outset of treatment, and from three to six months after the termination of treatment 20 per cent of these remained seropositive and 8 per cent had doubtful reactions. Most patients were followed for six months, with but 1 exception, patients with infectious or latent syphilis who were followed had complete serologic reversal. There were three serologic relapses in the group.

As a result of extensive experimentation on animals and in an effort to treat early syphilis intensively yet safely, Eagle [53] enlisted the aid of a number of clinics to carry out treatment for a period of twelve weeks. Among other reasons, his paper is particularly valuable for the inclusion of a sound statistical method of approach, for which details are given. He summarizes the results of his study as follows:

1. A total of 4,823 patients, including 3,394 cases of primary and secondary, 1,190 of latent and 159 of recurrent or relapsing syphilis, have been treated and with triweekly injections of mapharsen at approximately 1 mg. per kilogram per injection, with a maximum of 80 mg. and a minimum of 40. Two thirds of the patients were given concomitant weekly injections of a bismuth compound, usually bismuth subsalicylate (0.2 Gm.).

2. Treatment had to be interrupted because of toxic reactions in a total of 106 patients. Thirty-nine of these were serious reactions, with jaundice the most common complication. Four patients died. It is believed that at least two of these deaths were preventable and the mortality of the triweekly schedule is on the order of 1: 2,000. The incidence of toxic reactions was highest in young Negro women, and there were no deaths in the 2,583 men.

52. Goldblatt, S.: Intensive Ambulatory Therapy of Syphilis: Thirty Day Mapharsen Technic, Arch. Dermat. & Syph. **49**:403 (June) 1944.

53. Eagle, H.: The Treatment of Early and Latent Syphilis in Nine to Twelve Weeks with Triweekly Injections of Mapharsen: A Preliminary Analysis of the Results in the First 4,823 Cases, J. A. M. A. **126**:538 (Oct. 28) 1944.

3. Triweekly injections of mapharsen alone, without bismuth, gave uniformly poor therapeutic results, regardless of dosage.

4. Triweekly injections of mapharsen in conjunction with weekly injections of bismuth proved highly effective. In patients receiving an average total of 1,600 mg. (21 mg. per kilogram or more) plus an average total of nine injections of bismuth, the cumulative percentage of treatment failure was 9.3 and the cumulative percentage of "cure" fifty to sixty weeks after the beginning of treatment was 82 per cent. A decrease in either mapharsen or bismuth to less than these amounts resulted in a higher proportion of treatment failure.

5. Although these results are tentative, based on the prolonged observation of as yet a small proportion of the total patients treated, it is believed that triweekly injections of mapharsen at approximately 1 mg. per kilogram, combined with weekly injections of 0.2 Gm. of bismuth subsalicylate and continued for nine to twelve weeks, will probably "cure" 85 to 90 per cent of cases of early syphilis.

6. (*a*) The initial reagin titer affected the rate at which seronegativity was obtained but did not affect the ultimate percentage "cured." (*b*) Within fairly wide limits (fifty-four to eighty-one days), the total duration of treatment also had no effect on the end results. Within that time period occasional lapses in treatment or smaller individual dosages could be ignored, provided the patient eventually received the scheduled total amount of drug. (*c*) With equal amounts of treatment, secondary syphilis gave significantly more treatment failures than did seropositive primary syphilis.

7. The efficacy of this schedule in the prevention of congenital syphilis, and its efficacy in latent syphilis, are under continued study.

The cooperating clinics of New York and the Midwest [54] have analyzed results for a group of 4,351 patients treated intensively for early syphilis. Only those patients were chosen whose infection was of less than four years' duration either with or without active manifestations of the disease. These patients were treated during the period from 1933 to 1943 inclusive. The analysis of results, however, deals only with primary or secondary syphilis. Six different methods of treatment are analyzed: namely, slow intravenous drip, neoarsphenamine; slow intravenous drip, oxophenarsine hydrochloride; rapid intravenous drip, oxophenarsine hydrochloride; multiple syringe injection, oxophenarsine hydrochloride; multiple syringe injection, oxophenarsine hydrochloride plus typhoid vaccine; multiple syringe injection, arsphenamine, and other miscellaneous methods (a very small group).

This work is well summarized by the anonymous authors as follows:

1. The therapeutic results in a group of 4,351 massive arsenical treatment for syphilis have been studied.

2. It was found that the best results (excluding the highly reactive slow intravenous drip administration of neoarsphenamine) followed the use of multiple syringe injection of mapharsen combined with typhoid vaccine.

54. Massive Arsenotherapy for Syphilis: United States Public Health Service Evaluation, Cooperating Clinics of New York and Midwestern Group, J. A. M. A. **126**:554 (Oct. 28) 1944.

3. The most effective massive arsenotherapy yields 85 to 90 per cent of satisfactory results in primary syphilis and 70 per cent in secondary syphilis.

4. About 5 to 6 per cent of the primary cases relapsed and 10 to 13 per cent of the secondary cases.

5. Patients treated when the titer of the Kahn quantitative test on the blood was 20 units or below experienced more frequent satisfactory results and fewer clinical relapses than did cases with a titer greater than 20 units.

6. Results were slightly better among patients receiving larger doses of arsenicals than among those receiving smaller doses.

The administration of bismuth during the period of treatment appeared to improve the results obtained.

8. The following differences in response to treatment were noted: Patients over 25 years of age responded better than those under 25; males responded better than females; whites responded better than nonwhites.

9. Least satisfactory results to treatment were obained among young nonwhite females.

10. Acute encephalopathy was observed in 7.1 per thousand treatments. Of these 3.2 per thousand were fatal and 3.9 per thousand were followed by recovery. No difference could be demonstrated between treatments with regard to the frequency of this type of reaction.

Alexander and Schoch,[55] who have had much personal experience in the intensive treatment of early syphilis, review some of the more important contributions to this subject and conclude that longer term methods of intensive arsenotherapy of early syphilis, which do not require hospitalization of patients, should be used in preference to the hazardous and highly technical short term methods. Results of treatment are satisfactory with all methods. The twenty-six week method used by the Army of the United States, the triweekly twelve week schedule suggested by Eagle[53] and perhaps the twenty to thirty day syringe method can be advocated for general use on ambulatory patients.

Thomas and Wexler[56] review the results of 2,144 courses of rapid treatment for early syphilis, utilizing oxophenarsine hydrochloride administered by the multiple syringe technic, with or without the addition of fever therapy induced by typhoid vaccine. The injection of more than 1 Gm. of oxophenarsine hydrochloride in a period of six to ten days was associated with toxic encephalopathy in over 1 per cent of the patients treated. There were 3 deaths in 909 courses of treatment. The maximum daily dose of oxophenarsine hydrochloride was, therefore, subsequently fixed at 1 mg. per kilogram of weight, and the period of treatment was extended to at least ten days.

55. Alexander, L. J., and Schoch, A. G.: Intensive Arsenotherapy of Early Syphilis: Experience with over 1,300 Treated Patients, and a Review of the Literature, Clinics **3**:960 (Dec.) 1944; Newer Developments in Syphilis Therapy, South. M. J. **37**:705 (Dec.) 1944.

56. Thomas, E. W., and Wexler, G.: Review of 2,144 Courses of Rapid Treatment for Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **28**:529 (Sept.) 1944.

Combined Fever and Arsenotherapy.—In formulating their schedules of therapy in a later paper, Thomas and Wexler [57] consider not only the total amount of oxophenarsine hydrochloride which can safely be given in five to ten days but also the maximum single dose which can prudently be given at daily intervals. It was found that the maximum single dose of oxophenarsine hydrochloride per day was practically 1 mg. per kilogram of weight and the minimum period of treatment ten days. With such a schedule, the average patient received ten daily injections of about 60 mg. of oxophenarsine hydrochloride. To reenforce treatment with this low dosage, four fever treatments were given on the second, fourth, sixth and eighth days, produced by the intravenous injection of typhoid-paratyphoid combined vaccine. The first fever was induced with an injection of 0.1 cc. of vaccine, the second with 0.2 cc., the third with 0.4 cc. and the last with 0.6 cc. From one and one-half to two hours after each of these injections a booster dose was administered, usually of an equal amount. Although the fever response to this amount of vaccine varied, it generally caused a temperature of 104 F. for about four hours. Later bismuth was added to the scheme of treatment, and 0.1 Gm. of bismuth subsalicylate in oil was administered on the first, third, seventh and tenth days of therapy.

By May 1, 1944, 1,163 courses of treatment had been given according to this plan, without a single fatality. There were only 3 cases of mild encephalopathy and 1 case of granulocytopenia, from which the patient completely recovered. However, by the time 1,181 courses of treatment were completed there was 1 fatality, from hemorrhagic encephalitis. Therefore, in 1,181 treatments there were 4 cases of encephalopathy (0.34 per cent) and 1 death (0.08 per cent).

There were 772 patients with early syphilis treated. However, only 435 (56.3 per cent) had been followed from six to thirty-eight months. The results for 351 (80.7 per cent) were probably favorable.

Jones and his co-workers [58] report further observations on the one day treatment of early syphilis (combined fever and chemotherapy). Three methods have been given clinical trial. Schedule A consisted of 1 mg. of oxophenarsine hydrochloride per kilogram of weight, administered during the induction period of the fever. With schedule B, 1 mg. of oxophenarsine hydrochloride per kilogram of weight was injected in the evening prior to fever therapy, and a second injection, this time in the amount of 1.5 mg. per kilogram of weight, administered at the termination of fever. In schedule C, 2 mg. of oxophenarsine hydrochloride per kilo-

57. Thomas, E. W., and Wexler, G.: Combined Fever and Arsenotherapy in the Intensive Treatment of Early Syphilis, J. A. M. A. **126**:550 (Oct. 28) 1944.

58. Jones, N.; Hundley, J. L., and Walker, A..E.: Further Observations on One Day Treatment of Syphilis with Fever and Mapharsen, New York State J. Med. **45**:277 (Feb. 1) 1945.

gram of weight was administered at the termination of fever. With all three schedules, fever therapy consisted of five hours at a body temperature of 41.1 C. (106 F.).

The results of these three methods of therapy were as follows: Seventy-eight patients were treated according to schedule A and followed for twenty-two to thirty months; of these, 15 (19 per cent) had a clinical relapse and 1 a serologic relapse; 6 additional patients were thought to have been reinfected. Of 137 patients treated with schedule B and followed for twelve to twenty-two months, 13 (10 per cent) had a clinical relapse and 3 (2 per cent) showed serologic relapse; 2 patients were considered probably to have been reinfected. Two hundred and six patients were treated according to schedule C and observed for three to nine months; 16 (8 per cent) of these have shown clinical relapse during this short period of follow-up, and 5, serologic relapse. Only half the patients in this group, however, had symptomatic early syphilis, the others having early latent syphilis. The percentage of seroresistant patients is not indicated, nor does the report indicate the percentage of patients lost from observation.

During the period from 1932 to 1940 Kendell and his co-workers [59] treated 77 patients with primary or secondary syphilis with combined artificial fever and chemotherapy. During the first six years the course consisted of approximately fifty hours of fever maintained at an average temperature of 105.8 F. (rectal), usually given in ten weekly sessions of five hours each. From 1937 to 1940 the course comprised an average of twelve shorter sessions (three hours), usually at more frequent intervals, for an average total of thirty-six hours of fever maintained at the same average temperature. The two groups responded similarly. The authors do not provide details as to the chemotherapy used for these patients.

Of the 77 patients 17 were lost from observation. The remaining 60 patients were followed for two to ten years. Eight patients with seronegative primary syphilis remained clinically and serologically negative. Of the 24 patients with seropositive primary syphilis, 22 exhibited a rapid and progressive decline to negativity, both clinically and serologically. Of the 20 patients with early secondary syphilis all but 2 achieved clinical and serologic negativity after treatment. In the group of 8 patients with secondary manifestations occurring during the first or the second year of the disease, 5 responded both clinically and serologically.

In 1940 the authors began an investigation to determine whether it might be possible to cure syphilis in one day. Thirty-seven patients with unequivocal early syphilis, positive on dark field examination,

59. Kendell, H. W.; Rose, D. L.; Miller, E., and Simpson, W. M.: Artificial Fever and Chemotherapy in Early Syphilis, Arch. Phys. Med. **26**:76 (Feb.) 1945.

were included in this study. Six had secondary syphilis, and the remaining 31 had primary syphilis. The following treatment was instituted:

Just before the fever treatment was begun, 0.256 Gm. of bismuth subsalicylate was administered. The patient was then placed in the hypertherm and given one ten hour session of fever at 106 F. (rectal). Seven patients received 240 mg. of oxophenarsine hydrochloride by intravenous drip during the fever session. This procedure was later changed in favor of administration of the drug by syringe in doses of 40 or 60 mg. to a total of 120 mg. to 160 mg. No other treatment was administered subsequently. Six patients were followed for four to six months; 29 were followed for six months to two and one-half years; 1 patient was lost to follow-up, and 1 died as a result of treatment. All of the 35 patients who were followed are now clinically and serologically negative.

The authors say that intensification of the fever-chemotherapy method as described increases complications, and they do not recommend this method as routine for the treatment of early syphilis.

Schwemlein, Kendell and Craig [60] present the methods of charting used during the past twenty-three months at the Chicago Intensive Treatment Center in the artificial fever-chemotherapy of 1,667 patients with early syphilis. The actual chart utilized, with explanatory comments, presented in the original article, does not lend itself to reproduction. The value of this system is that it presents a quick summary of the patient's condition under treatment every fifteen minutes. As the readings are chronologic, valuable information is afforded for the investigation and control of the patient's water and electrolyte balance.

The results of treatment of early syphilis with bismuth alone are reported by Sharp, Dickerson, Sevier and Branch.[61] The drug, bismuth ethylcamphorate, was injected intramuscularly twice weekly in 2 cc. doses (80 mg. of metallic bismuth). One group consisting of 41 patients with untreated early syphilis were treated in this manner for eight weeks. A second, of 30 patients with infectious (9 patients) or serologic (21 patients) relapse following intensive arsenotherapy, were so treated for thirteen to sixteen weeks. At the time of this report all patients had been followed a minimum of eight months. Of the first group, all 41 patients were considered to have attained clinical and serologic "cure." Of the second group (30), all had remained clinically well, and all but 5 had become seronegative. No toxic reactions were observed.

(To Be Concluded)

60. Schwemlein, G. X.; Kendell, H. W., and Craig, R. M.: Artificial Fever-Chemotherapy: III. Charting Procedures, Arch. Phys. Med. **26**:8 (Jan.) 1945.

61. Sharp, J. W.; Dickerson, M. S.; Sevier, M., and Branch, W.: Intensive Bismuth Ethylcamphorate Treatment of Early Syphilis and Its Use in Relapse Cases, Urol. & Cutan. Rev. **48**:613 (Dec.) 1944.

Book Reviews

The Avitaminoses: The Chemical, Clinical and Pathological Aspects of the Vitamin Deficiency Diseases. By Walter H. Eddy, Ph.D., and Gilbert Dalldorf, M.D. Price, $4.50. Pp. 438, with 40 tables and 46 figures. Baltimore: The Williams & Wilkins Company, 1944.

Fifteen years ago Dr. Eddy wrote a book entitled "The Vitamine Manual." A comparison of that book with the present, or third, edition, under a new title, will indicate that this new edition is larger and much more complete than the first, chiefly because of the addition of most important pathologic and somewhat less important clinical discussions of vitamin deficiency diseases. Secondly, the third edition indicates the tremendous amount of work, both clinical and in the laboratory, which has been done by investigators throughout the world in the study of vitamins and the avitaminoses.

This edition is divided into three parts, the first dealing with the various vitamins known to the clinician by letters and including a chapter on the nature and function of vitamin E and one on vitamin K, as well as a similar chapter on "bios nutralites." Vitamin B as such is not included among the vitamins, but chapters are devoted to thiamine, riboflavin, niacin and pyridoxine.

Part two is devoted to the avitaminoses and describes the clearcut syndromes which arise as a result of an insufficient amount of this or that vitamin in the dietary intake, such as pellagra, scurvy, rickets or other vitamin deficiency disorders. It seems rather a pity that the author has not included a section on multiple deficiencies, which do not present a clearcut syndrome of any one vitamin deficiency but which in the aggregate, because of the inadequate intake of numerous vitamins and other necessary nutritional elements, present a bizarre picture of disease or of functional disorder.

The third portion of the book has to do with technical methods of vitamin assay; then there follows a bibliography of some 32 pages and an appendix indicating the vitamin content of various foods and a second table which lists the known facts concerning the as yet incompletely assayed members of the B complex, those other than thiamine, riboflavin and niacin (nicotinic acid).

One cannot do otherwise than speak well of this book. The clinician can use it, and the man in the laboratory can obtain much information from it. Its success seems assured.

Bronquiectasias. By Dr. Mariano R. Castex, Professor of Clinical Medicine, Faculty of Medicine of Buenos Aires, and Dr. Egidio S. Mazzei, Assistant Professor of Clinical Medicine of La Plata. Paper. Price not given. Pp. 77, with 19 illustrations. Barcelona-Buenos Aires: Salvat Editores, S. A.

This monograph, one of the *Manuales de Medicina Practica*, gives a vivid description of the clinical types of bronchiectasis seen in Argentina, including roentgenographic observations and discussions of the physiopathology of the disease, certain pathologic features and therapeutic methods. The structure of the bronchi was studied by bronchography with opaque oil, by tomography and by a special photographic technic called "broncorrelievografía," by which means minute details of the bronchi filled with opaque oil were sharply demonstrated. The morphologic types of bronchiectasis are classified as (1) cylindric, (2) ampullaceous, (3) saccular and (4) maniliform. The authors found that the acquired form occurred more frequently than did the congenital, and they postulate that chronic infections are the most important causes of the acquired forms. No favorite methods of

therapy are especially advocated. Bronchoscopic examinations or treatments were apparently not often utilized. No enthusiasm is expressed for lobectomy.

An extensive bibliography is appended. An unusually large proportion of the references are to the French literature.

It is pleasant to receive such well prepared material from our southern neighbors, and it is hoped that similar articles in the future will contain statistical information as regards incidence, attack rate, percentage of patients treated by various methods and results obtained, mortality and so forth, so that one may compare similar problems in the various countries.

A Synopsis of Medicine. By Sir Henry Letheby Tidy, K.B.E., M.A., M.D., B.Ch. (Oxon.), F.R.C.P. (Lond.). Eighth edition. Price, $7.50. Pp. 1,215. Baltimore: The Williams & Wilkins Company; Bristol: John Wright & Sons, Ltd., 1945.

It is rather interesting to note that in the preface to the first edition of this book, which appeared in 1920, the author stated that there was a long interruption due to the war, the book appearing several years after the original date of its intended publication. In the eighth, and present, edition it is noted that the revision of this edition has been accomplished with difficulty; ". . . the premises of the publisher have been twice damaged severely by enemy action, on one occasion unfortunately with serious loss of life. Several thousands of copies of a reprint were destroyed by enemy action." It seems remarkable that this book of Tidy's has successfully survived two world wars, both of which interfered materially with its publication.

This is a standard synopsis which has been used for many years by practitioners and students of medicine. The reviewer has little quarrel with the author concerning the material contained between the two covers of this book. One definite criticism would be that the space assigned to the various diseases is by no means proportional to their importance. This is a real criticism, as the book is certainly too large in its present form and is difficult to handle. In support of the statement of the disproportionate amount of space given to certain diseases, it might be noted that of the first 50 pages (chapter 1), 34 are devoted to typhoid and 14 to diphtheria, while erysipelas has one page and septicemia, pyemia and toxemia taken as a whole have a little over a page devoted to them. Lobar pneumonia occupies 17 pages, whereas a page only is given to primary atypical pneumonia, which, in the United States at least, has been seen much more frequently of late than has the classic pneumococcic pneumonia.

There are a few statements which are incorrect and undoubtedly will be revised in the next edition. As an example, Streptococcus scarlatinae is given as the cause of scarlet fever, whereas it is only one of a number of hemolytic streptococci which may produce the symptoms of this disease.

The book purely as a synopsis is highly recommended to persons who wish to make use of this type of publication. Certainly it will prove a timesaver to the general practitioner, as the author indicates in his preface. Whether or not the immense amount of material contained in the book, for the most part presented in telegraphic style, could be assimilated and remembered in a short time by the "worried student whose final examinations are within sight" is a question.

Hayfever Plants. By Roger P. Wodehouse. Price, $4.75. Pp. 245. Waltham, Mass.: The Chronica Botanica Co.; New York: G. E. Stechert and Company, 1945.

This thorough compendium deals in a systematic way with the botany and geography of the various plants concerned with hay fever. Supplemented by regional surveys which make up the latter part of the book, it is an invaluable encyclopedia for the physician who deals with allergic disease. There are numerous illustrations, a bibliography and an index.

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